

Exercise Training by Neuromuscular Stimulation in Chronic Heart Failure

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To Izzy, Angus and Tara

and to any that may follow

love always

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Declaration

The preparation of this manuscript has been performed solely by myself with no text incorporated from the work of any other author. Other than study 1, the collection, analysis and interpretation of data presented in this thesis is entirely my own. Approximately 50% of the data collection for study 1 was performed by Dr Stuart Harris; however, all subsequent data collection, data analysis and the preparation of the published manuscript for this study was performed by myself.

This thesis has not been submitted for any other degree or higher qualification.

Condensed Abstract

Background.

Conventional exercise training in chronic heart failure (CHF) is safe and beneficial. Training is therefore recommended in a number of guidelines although the data upon which these recommendations are based are drawn from trials enrolling highly selected groups of CHF patients. Extrapolation of these data to a wider CHF population is difficult. Additionally, the optimal mode of training and the timing of introduction of training during a CHF patient's illness pathway is unclear. Applicability of conventional training regimes to the wider population is uncertain. This thesis explores the differing characteristics of trial and general CHF populations and describes the utility of a novel form of exercise training, neuromuscular electrical stimulation of the legs for both stable patients and those with recently decompensated symptoms, a group normally excluded from exercise training trials.

Methods.

Studies 1-3 randomise stable patients to conventional bicycle training (Bike) or neuromuscular stimulation (NMS) of quadriceps and gastrocnemius leg muscles. A 6-week training programme is undertaken with functional performance assessed by 6-minute walk (6MW), quadriceps strength and fatigue testing, cardiopulmonary exercise testing and quality of life scoring. Body composition is assessed further in study 2 using dual-energy X-ray absorptiometry. Inflammatory markers are assessed before and after training in study 3. Study 4 is a controlled trial of NMS and Bike training including

stable (S-CHF) and recently decompensated (RD-CHF) patients, with performance testing before and after a period of training. Study 5 explores the characteristics of a large group of CHF patients admitted to hospital with heart failure and compares the characteristics of these patients with those included in the exercise training trial described in study 4 and also with those patients included in a recent meta-analysis of exercise training trials.

Results.

Improvements in 6MW, treadmill exercise time, quadriceps strength and fatigue were observed following both Bike and NMS training for stable patients in study 1. In study 2, a significant improvement in peak VO_2 following bike training but not NMS was observed when corrected for lean muscle mass. No change in body composition following training was observed. Pro-inflammatory state was attenuated following conventional training with a significant fall in $\text{sTNF}\alpha_{\text{r2}}$ in the Bike group only. NMS training resulted in significant improvement in NT-pro BNP when compared with controls and Bike patients in study 4. Overall, exercise training appeared to be effective when RD-CHF patients were included. Study 5 demonstrated that only 6.7% of the screened population was suitable for inclusion in the exercise training trial in study 4. Eligible patients were younger, more likely to be male, had fewer comorbidities and were on more optimal CHF medication than the non-eligible patients despite similar symptoms. The characteristics of the eligible patients were similar to those included in the large meta-analysis.

Conclusions.

NMS exercise training appears safe and effective in stable CHF patients, although it differs from Bike training in its effects on markers of inflammation. Body composition did not change following training despite functional improvements, implying qualitative changes in peripheral muscle. RD-CHF patients may benefit from training but recruitment into a trial of exercise training is difficult. NMS is more easily delivered than Bike training and it may be a useful alternative or bridging therapy for those who cannot exercise conventionally. Extrapolation of data presented in this thesis and that published in the literature needs to be viewed critically in the context of the wider CHF population as standard inclusion and exclusion criteria application in addition to the psychosocial features of those volunteering for trials results in substantially different population characteristics.

Publications resulting from thesis

Chapter 4:

Harris S, **LeMaitre JP**, Mackenzie DG, Fox KAA, Denvir MA. A randomised study of home-based electrical stimulation of the legs and conventional bicycle exercise training for patients with chronic heart failure. *European Heart Journal* 2003 **24**:871-8.

Chapter 5:

LeMaitre JP, Harris S, Hannan J, Fox KAA, Denvir MA Maximum oxygen uptake corrected for skeletal muscle mass accurately predicts functional improvements following exercise training in chronic heart failure. *European Journal of Heart Failure* 2006 **8**:243-8.

Chapter 6:

LeMaitre JP, Harris S, Fox KAA, Denvir MA. Change in circulating cytokines following two forms of exercise training in chronic stable heart failure. *American Heart Journal* 2004 **147**:100-5.

Smart NA, **LeMaitre JP**, Larsen AI, Ferraz A. Influence of exercise training efficacy on change in pro-inflammatory cytokine profile in systolic heart failure. *In press. European Journal of Cardiac Rehabilitation and Prevention.*

Chapter 7:

LeMaitre JP, McKee SP, Fox KAA, Denvir MA. Safety and efficacy of functional electrical stimulation and conventional physical training in recently decompensated heart failure patients. *Manuscript submitted.*

Chapter 8:

LeMaitre JP, McKee SP, Fox KAA, Denvir MA. Participants suitable for inclusion in exercise training trials are substantially different from the general heart failure population. *Manuscript in preparation.*

Presentations to learned societies

LeMaitre JP, Harris S, Mackenzie G, Fox KAA, Denvir MA. Influence of body composition on functional capacity in chronic heart failure. *Presentation to Scottish Cardiac Society, 14.09.01.*

LeMaitre JP, Harris S, Mackenzie G, Fox KAA, Denvir MA. Limb skeletal muscle mass predicts exercise capacity and ventilatory response in chronic heart failure patients. *European Journal of Heart Failure 2002 S1:10. Presentation to European Society of Cardiology Heart Failure Update meeting, 9.06.02*

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from. *Presentation to European Society of Cardiology Annual Congress, 4.9.07*

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Abbreviations

6MW	6-minute walk
ACC	American College of Cardiology
ACE	Angiotensin converting enzyme
ACEi	Angiotensin converting enzyme inhibitor
ADH	Anti-diuretic hormone / arginine vasopressin
AHA	American Heart Association
AIRE	Acute Infarction Ramipril Efficacy Study (trial)
ANP	Atrial natriuretic peptide
ARB	Angiotensin II receptor blocker
AVP	Arginine vasopressin / anti-diuretic hormone
BNP	Brain natriuretic peptide
Ca ²⁺	Calcium ion
CHF	Chronic heart failure
CHFQ	Chronic heart failure questionnaire

CI	Confidence intervals
CNP	Clearance natriuretic peptide
CO	Cardiac output
CS	Cardioselective
DFI	Dyspnoea-fatigue index
EDP	End diastolic pressure
EDV	End diastolic volume
EF	Ejection fraction
ESC	European Society of Cardiology
ESV	End systolic volume
ET-1	Endothelin 1
Global QoL	Global quality of life
GP	General practitioner
HPPQ	Heart patients' psychological questionnaire
HR	Hazard ratio

hs-CRP	High-sensitivity C-reactive protein
ICD	Implantable cardiac defibrillator
IL-6	Interleukin 6
LV	Left ventricular
MLWHF	Minnesota living with heart failure questionnaire
MMAS	Morgan Medical Analysis Suite
MRI	Magnetic resonance imaging
NHP	Nottingham Health Profile
NMS	Neuromuscular stimulation
NT pro-BNP	N-terminal pro brain natriuretic peptide
NYHA	New York Heart Association
OR	Odds ratio
OUES	Oxygen uptake efficiency slope
PAS	Physical activity score
QLQ-HF	Quality of life questionnaire – heart failure

RD-CHF	Recently decompensated chronic heart failure
RR	Relative risk
SAGWB	Self-assessment of general well-being
SAVE	Survival and Ventricular Enlargement Study (trial)
S-CHF	Stable chronic heart failure
SG	Standard Gamble test
SIP	Sickness impact profile
SOC	Sense of coherence scale
SOLVD	Studies of Left Ventricular Dysfunction (trial)
sTNF _{r1}	Soluble tumour necrosis factor alpha receptor 1
sTNF _{r2}	Soluble tumour necrosis factor alpha receptor 2
SV	Stroke volume
SVR	Systemic vascular resistance
TNF α	Tumour necrosis factor alpha
TRACE	Trandolapril Cardiac Evaluation (Trial)

1 Abstract

1.1 Introduction

Conventional exercise training is safe in chronic heart failure (CHF) and beneficial for a wide range of outcome measures including exercise performance, aerobic capacity and quality of life. From one randomised study, one meta-analysis and a Cochrane review, there is emerging evidence of a possible mortality benefit and reduction in hospitalisation following training which may attenuate the major socioeconomic burden that heart failure presents. Training is recommended in a number of guideline documents but data on which these recommendations are based are drawn from trials of highly selected patients. Translation of findings to a wider heart failure population is difficult. In this thesis, data are presented exploring a novel method of exercise delivery, neuromuscular electrical stimulation (NMS). Study 1 is a pilot study of NMS vs. bicycle exercise in stable CHF patients. Study 2 explores the differing effects of NMS and conventional training on body composition and exercise performance to investigate the hypothesis that quantitative changes in muscle are responsible at least in part for the functional gains observed. Study 3 explores the role of NMS training in the attenuation of the pro-inflammatory response in CHF. Study 4 is a randomised controlled trial of NMS and conventional exercise and follows on from the pilot study, study 1. Patients who have recently been discharged from hospital following an acute decompensation of their heart failure, a group previously not considered for training, are included and outcomes compared with the stable patient, the group traditionally enrolled in training

studies. Study 5 explores the characteristics of stable, recently-decompensated and published trial populations of heart failure patients compared with the wider CHF population from which they are recruited as substantial differences are likely to exist, limiting the interpretation of published findings.

1.2 Methods

Studies 1-3 randomised stable patients to conventional bicycle ergometer training or neuromuscular stimulation of the quadriceps and gastrocnemius muscles of the legs. Exercise was performed daily for 6 weeks. Functional performance was assessed by 6-minute walk (6MW), quadriceps strength and fatigue measurement and cardiopulmonary exercise test. Quality of life was assessed with the Minnesota 'Living with Heart Failure' questionnaire. Body composition was measured by dual-energy X-ray absorptiometry (DEXA scanning). Inflammatory state was assessed by measurement of interleukin-6 (IL-6), high sensitivity C-reactive protein (hs-CRP), tumour necrosis factor α (TNF α) and the soluble TNF α receptors, sTNF α_{r1} and sTNF α_{r2} . Studies 4 and 5 recruited patients following a recent decompensation of their heart failure (RD-CHF) in addition to stable CHF patients (S-CHF). RD-CHF commenced NMS or conventional cycle ergometer training within 4 weeks of hospital discharge according to the same protocol as S-CHF patients. In study 5, 672 CHF patients were screened either following hospital admission or following attendance at a hospital clinic. Baseline characteristics of patients scrutinised in a recent meta-analysis of CHF exercise training trials were compared with the screened population and the S-CHF and RD-CHF groups.

1.3 Results

In study 1, 46 stable patients were randomised. Conventional cycle ergometer exercise and NMS resulted in significant improvement in 6MW, treadmill exercise time, quadriceps strength and fatigue. Peak VO_2 in both groups was unaltered following training.

In study 2, 36 stable patients were randomised. Significant improvement in peak VO_2 corrected for lean muscle mass was seen following conventional cycle ergometer training but not NMS. Both forms of training resulted in similar improvements in treadmill exercise time, leg strength and 6MW. No significant alteration following training was observed in body composition.

In study 3, 46 stable patients were randomised. Pro-inflammatory state appeared to be attenuated by conventional cycle ergometer training but not by NMS, with a significant decrease in $\text{sTNF}\alpha_{12}$ in the bike group only.

In study 4, 40 patients were recruited (15 S-CHF and 25 RD-CHF). Exercise training with conventional cycle ergometer or NMS resulted in significant gains in NYHA functional class, 6MW, VO_2 at anaerobic threshold, oxygen uptake efficiency slope, VE/VCO_2 slope, NT-pro BNP, quadriceps strength and treadmill exercise time when compared with controls. NMS training for RD-CHF patients appeared to result in a greater reduction in NT-pro BNP in the NMS group compared with conventional training and control patients.

In study 5, 672 patients were screened. Only 6.7% were eligible to participate in a trial of conventional vs. NMS exercise training when standard inclusion and exclusion criteria were applied. Of the 5.06% subsequently randomised only 3.42% of the originally screened population were able to complete the study. Eligible patients were younger, had similar NYHA class, had fewer comorbidities and were more likely to be treated with ACEi, B-blockers, aldosterone antagonists and digoxin than the non-eligible population. Younger and male patients were over-represented in the published meta-analysis also.

1.4 Conclusions

NMS exercise training appears safe and effective in stable CHF patients, although it does differ from conventional cycle ergometer training in its effects on markers of inflammation. No change in body composition was observed following either form of training in stable patients despite functional improvements, implying qualitative rather than quantitative changes in peripheral muscle. RD-CHF patients may benefit from training but recruitment into and maintenance within a trial of exercise training is difficult. NMS appears to be a more practical training modality than conventional cycle ergometer training and benefits for RD-CHF patients following NMS are observed. NMS may be a useful alternative for those CHF patients who cannot exercise conventionally due to limited functional capacity. Alternatively, it could be useful as a bridging therapy before a more conventional regime can be adopted. The role of early exercise training for the recently decompensated patient remains uncertain. Extrapolation of the trial data presented in this thesis and that published in the literature

needs to be viewed critically in the context of the wider CHF population as standard inclusion and exclusion criteria application in addition to the psychosocial features of those volunteering for trials results in substantially different population characteristics.

2 Introduction

Heart failure is common and lethal. It represents a major health care burden for the 21st century as the population ages and patients with ischaemic heart disease show improved survival. Yet the mechanisms by which the syndrome develops and progresses are incompletely understood. Advances have been made over the past 20 years in the treatment of heart failure, particularly with respect to the angiotensin converting enzyme inhibitor and beta-blocker classes of drugs; more recently, advances have been made with cardiac resynchronisation therapy and automated implantable defibrillators. Despite this however, the mortality in heart failure remains very high and rivals the mortality associated with some neoplasms. Clearly, our understanding of this condition remains incomplete and other as yet unidentified pathological mechanisms exist in heart failure which contribute to the progression of this debilitating syndrome. Research continues around the globe to promote our understanding in all aspects of heart failure, from basic science and genetic studies through to population based data.

A key feature of the syndrome of heart failure is exercise intolerance, due to fatigue and breathlessness. Over the last 10 years or so, preliminary evidence has emerged suggesting the symptomatic benefit of exercise training for patients with heart failure. Issues regarding the potential role for training in certain patient groups form the main focus for this thesis. Exercise training regimes undertaken in previously published work differ, but mainly involve conventional forms of training. A major drawback, of course, is the difficulty in targeting appropriate patient groups for exercise prescription given the

elderly, detrained and demotivated nature of the heart failure population and conventional forms of exercise are unsuitable for those patients with more advanced disease. Non-conventional forms of exercise training which require less physical effort on the part of the participant may be of particular use in this circumstance and research on this topic will be presented below. To begin with, however, the syndrome of heart failure will be introduced and defined, following which the current knowledge regarding epidemiology and pathogenesis will be detailed. Subsequently, the current evidence for exercise training in heart failure will be presented and the rationale for the design of studies presented in this thesis will be explained.

2.1 Definition

2.1.1 Basic definitions

Heart failure is a complex clinical syndrome rather than a disease in itself and manifests with symptoms of fatigue, exercise intolerance, breathlessness, oedema and sometimes cachexia. It can be defined as a condition in which the heart loses its ability to efficiently eject sufficient blood to meet the metabolic demands of the body. The inefficiency can be due to impaired contraction of the ventricles during systole secondary to disease of the myocardium (systolic heart failure) or due to impaired relaxation of the ventricles preventing adequate filling (diastolic heart failure). Aetiologies of heart failure are diverse and include ischaemic heart disease, cardiomyopathy, valvular heart disease and hypertension (Table 2.1). Simply put, heart failure is a syndrome which results from any structural or functional cardiac disorder which impairs the ability of the ventricle to fill

with or eject blood.

The terms right heart failure and left ventricular failure are sometimes used to indicate impairment of predominantly the right or left ventricle, respectively. Right heart failure is a clinical syndrome characterised by tissue congestion (including a raised jugular venous pressure, peripheral oedema, ascites and abdominal organ enlargement) with marked impairment of right ventricular systolic performance, usually with right

<i>Coronary artery disease</i>
<ul style="list-style-type: none">• Myocardial infarction• Ischaemia
<i>Hypertension</i>
<i>Cardiomyopathy</i>
<ul style="list-style-type: none">• Dilated• Hypertrophic / obstructive• Restrictive-for example, amyloidosis, sarcoidosis, haemochromatosis• Obliterative
<i>Valvular and congenital heart disease</i>
<ul style="list-style-type: none">• Mitral valve disease• Aortic valve disease• Atrial septal defect, ventricular septal defect
<i>Arrhythmias</i>
<ul style="list-style-type: none">• Tachycardia• Bradycardia (complete heart block, sick sinus syndrome)• Loss of atrial transport-for example, atrial fibrillation
<i>Alcohol and drugs</i>
<ul style="list-style-type: none">• Alcohol• Cardiac depressant drugs (e.g. calcium antagonists)
<i>"High output" failure</i>
<ul style="list-style-type: none">• Anaemia, thyrotoxicosis, arteriovenous fistulae, Paget's disease, bacteraemia / sepsis
<i>Pericardial disease</i>
<ul style="list-style-type: none">• Constrictive pericarditis• Pericardial effusion
<i>Primary right heart failure</i>
<ul style="list-style-type: none">• Pulmonary hypertension e.g., pulmonary embolism, cor pulmonale, primary pulmonary hypertension• Right ventricular infarction• Tricuspid incompetence

Table 2.1. Aetiology of heart failure

ventricular dilatation and severe tricuspid regurgitation. There are multiple causes including severe left heart failure, severe lung disease with pulmonary hypertension, primary pulmonary hypertension and right ventricular infarction.

Heart failure can also be classified as either acute or chronic and the term 'decompensated heart failure' is sometimes used to describe the worsening of previously stable chronic heart failure with the development of acute symptoms.

In summary, heart failure is a general term which encompasses multiple aetiologies, pathophysiological mechanisms and clinical presentations.

2.1.2 Staging and severity

Two methods of defining the severity of heart failure are generally used in clinical practice and will be used during this thesis. The most commonly reported scale is the

Class I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue or dyspnoea
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue or dyspnoea.
Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue or dyspnoea.
Class IV	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Figure 2.1. New York Heart Association classification of symptom severity

New York Heart Association (NYHA) classification (The Criteria Committee of the New York Heart Association, 1964, Figure 2.1). This classification is widely used to describe the functional capacity of patients with heart failure, i.e. symptoms, but gives no indication of the progression or aetiology of the syndrome. Critics of the NYHA system argue that the assessment of a patient's symptoms is subjective and varies between observers, and that symptoms for an individual patient can vary over short periods of time without necessarily indicating significant progression of the syndrome. Additionally, the classes of drugs used as therapy for heart failure are broadly similar between the NYHA classes. As such the American College of Cardiology / American Heart Association task force have recently proposed an additional staging system which takes account of the progressive nature of the syndrome and identifies stages at which specific therapies are appropriate (Hunt *et al.*, 2001). This scheme is designed to complement the NYHA symptom classification and is unidirectional – the syndrome will inevitably progress to stage D (Figure 2.2).

2.2 Epidemiology

Since a common definition is difficult to establish in heart failure, the epidemiology of the syndrome is difficult to fully delineate. Heart failure can be considered as a clinical entity, based on symptoms such as fatigue and breathlessness which, as discussed above, may be highly variable during an individual's disease course, or it can be considered with respect to the underlying pathology i.e. systolic or diastolic ventricular dysfunction. Asymptomatic patients with left ventricular systolic dysfunction are at risk of developing the syndrome of heart failure and represent an additional group. As such, it is

critical when discussing both the epidemiology of heart failure and the outcomes reported in clinical studies to be absolutely clear how heart failure has been defined, particularly given that patient groups involved in therapeutic intervention trials rarely have characteristics identical to that of the real disease population in the community. This is particularly true of trials involving exercise training, an issue which will be discussed further in chapter 8.

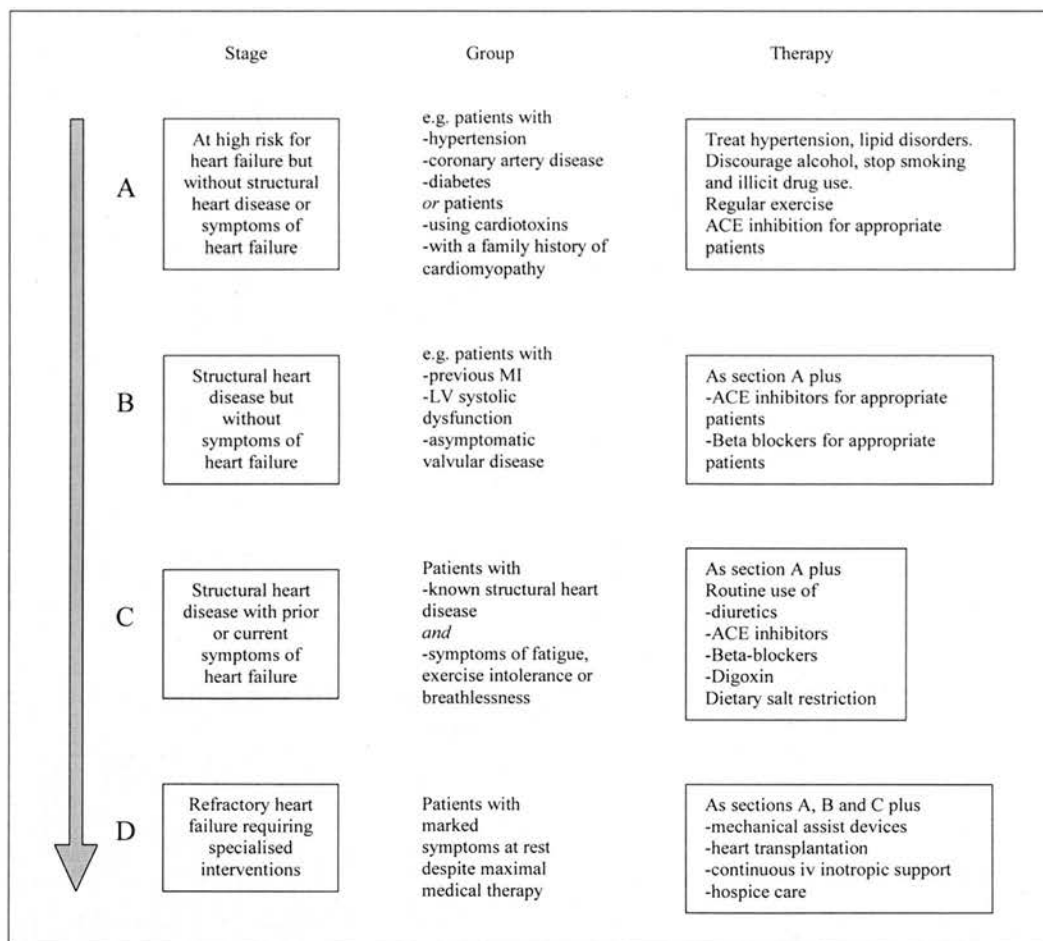


Figure 2.2. AHA/ACC staging system for chronic heart failure.

2.2.1 Prevalence

2.2.1.1 Clinical heart failure

Contemporary estimates of the prevalence of heart failure are sobering although the figures themselves should be interpreted with some caution. In the UK, prevalence is probably around 1% overall and Figure 2.3 summarises some reported prevalence rates. It can be seen from this that estimates do vary, primarily due to differing methodologies of data collection, and differing definitions of what heart failure actually is. An example of this problem is seen with the frequently quoted statistics from America: it is estimated that 4790000 individuals in the USA currently have heart failure. This is based on self reporting from the period 1988-1994 with correction for under-reporting and extrapolation to current population figures (National Health and Nutrition Examination Survey III, 1994). A more up-to-date self-reporting study from 1999 estimates that 2.4 million people in the US had been told they had heart failure (Ni, 2003). This was also based on questionnaire data; positive responses to a question asking if subjects had ever been told they had 'congestive heart failure' were seen in 0.1%, 1.1%, 3.6% and 5.5% of American people aged 18-39, 40-64, 65-74, 75-105, respectively. Naturally, these kinds of self-reporting based research are crude ways of estimating prevalence and methodological problems probably explain the wide variation in prevalence. A more recent American survey has estimated the prevalence of LV systolic impairment as 6% (moderate or severe LV systolic dysfunction 2%) and mild diastolic dysfunction as 21%, moderate or severe diastolic dysfunction as 7% (Redfield *et al.*, 2003).

The increasing prevalence of heart failure with increasing age is important to note, however, as this observation is made consistently in epidemiological studies of heart failure, for instance the data from the Framingham study reported in McKee, *et al.* (1971) where there was an estimated prevalence in the age groups 50-59, 60-69, 70-79 and >80 of 8, 23, 49 and 91 per 1000 – these figures were based on more robust clinical criteria (compared with questionnaire self-reporting) but reservations do exist regarding the ethnic homogeneity of the Framingham population and the era in which the data were collected (i.e. predating the modern trends in ischaemic heart disease survival and heart failure therapy). Again, similar age-related trends are seen with general practitioner-based observation studies (Parameshwar *et al.*, 1992) and population studies (Remes *et al.*, 1992; Rodeheffer *et al.*, 1993), although in only a small proportion of cases in these studies was a diagnosis of heart failure based on an objective measurement of left ventricular (LV) function. With more strict assessment of LV systolic dysfunction using echocardiography, the trend for increasing prevalence has been demonstrated in a Scottish population also (McDonagh *et al.*, 1997). Age-related trends have been confirmed in the latest report from the AHA statistics committee, as shown in Figure 2.3 (Rosamond *et al.*, 2007).

2.2.1.2 Systolic dysfunction.

Studies assessing the prevalence of LV systolic dysfunction have been carried out. In north Glasgow, the prevalence of LV systolic dysfunction, as defined as an ejection fraction of less than 30%, in a randomly selected population of men and women aged 25-74 was 2.9% overall (McDonagh *et al.*, 1997). Prevalence increased with age and

was more common in men than women (6.4% of men aged 65-74 compared with 4.9% of women). Overall, only 1.5% of those with LV systolic dysfunction had symptoms and this is an important issue as discussed in section 2.2.1.4.

2.2.1.3 Diastolic dysfunction.

Prevalence of diastolic dysfunction in the community is even harder to estimate as criteria for the definition of this subset of heart failure varies. Previously, diastolic dysfunction has been a diagnosis of exclusion, i.e., symptoms and clinical signs consistent with heart failure, but no objective evidence of abnormal left ventricular systolic function. Prevalence estimates vary (Vasan *et al.*, 1995) but a recent interim study analysis using echocardiographic criteria reports that in an American population over the age of 45 years and with an ejection fraction of greater than 50%, 5.3% of subjects had moderate to severe diastolic dysfunction and 16.6% had mild dysfunction (from Rodeheffer, 2002). Similarly, the Olmsted County data reported by Redfield, *et al.*

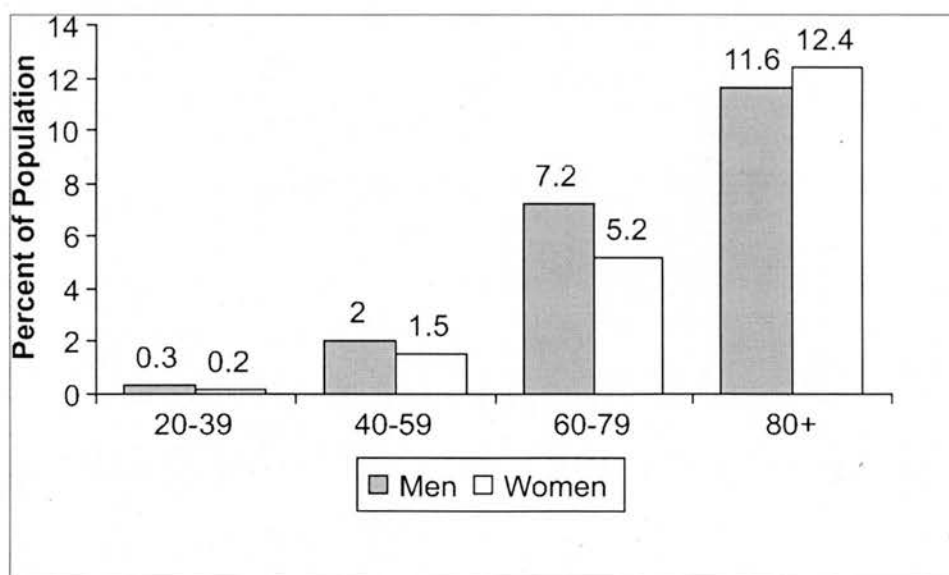


Figure 2.3. Age-related trends in heart failure prevalence. Adapted from Rosamond, *et al.* (2007)

(2003) identified mild diastolic dysfunction in 20.8%, moderate diastolic dysfunction in 6.6% and severe diastolic dysfunction in 0.7% of screened subjects, making diastolic dysfunction approximately as common as systolic dysfunction. However, diastolic dysfunction in these subjects was not commonly associated with symptoms despite being predictive of all cause mortality. The precise relation between these data and clinical syndromes and outcomes remains unclear, but early identification diastolic dysfunction may allow earlier treatment and perhaps delay or prevent progression from stage B to stage C of the heart failure syndrome.

2.2.1.4 Asymptomatic LV systolic dysfunction.

Asymptomatic LV systolic dysfunction is common and is probably as prevalent as symptomatic LV systolic dysfunction, although the estimates do vary and depend on a number of factors in the study design including the particular cut-off level of ejection fraction used to define dysfunction (Davies *et al.*, 2001; Devereux *et al.*, 2001; Mosterd *et al.*, 1999; Redfield *et al.*, 2003; Schunkert *et al.*, 1998) or whether qualitative assessments were used (Gottdiener *et al.*, 2002). For instance, in the North Glasgow study, 1.4% of the participants who had an ejection fraction less than 30% had no symptoms, increasing to 5.9% of those with an ejection fraction less than 35% (McDonagh *et al.*, 1997). Similarly, a recent assessment of the original and offspring Framingham cohorts over 40 years old and with no history of heart failure identified that 3% of participants overall had an ejection fraction of less than 50% (Wang *et al.*, 2003). In males it was more common (6%) compared with females (0.8%), probably due to an increased burden of ischaemic heart disease in men. There was increasing prevalence

with age (14.3% of those male subjects aged 80 and over).

The importance of asymptomatic LV systolic dysfunction lies in the natural history of this condition. In the above study of the Framingham cohorts, 26% of those with asymptomatic LV systolic dysfunction developed symptoms of heart failure over a mean follow-up period of 5 years and there was a clearly increased risk of death – age- and sex-adjusted hazard ratios for asymptomatic subjects with ejection fractions less than 50% and less than 40% were 1.9 and 3.1, respectively, compared with subjects without asymptomatic LV dysfunction. For comparison, subjects with symptomatic heart failure at baseline had a mortality hazard ratio of 5. Interestingly, 56% of those subjects with asymptomatic LV dysfunction at baseline who subsequently died had not developed symptomatic heart failure in the interim.

Other studies of the natural history of asymptomatic LV systolic dysfunction also identify increased cardiovascular or all-cause mortality in this group although event rates were low overall (Gottdiener *et al.*, 2002; McDonagh *et al.*, 2001). For large trials involving patients post-myocardial infarction and with degrees of LV systolic dysfunction, increased progression to symptomatic heart failure is also seen with mortality rates intermediate between those individuals with preserved LV systolic function and those with symptomatic heart failure at baseline (Kober *et al.*, 2000; Pfeffer *et al.*, 1992; Sharpe *et al.*, 1990; SOLVD Investigators, 1992).

These data highlight the importance of the inclusion of stage B in the American Heart Association guidelines as discussed in section 2.1.2. Treatments directed towards this

group may be helpful in preventing or delaying the progression to symptomatic heart failure and may reduce hospitalisation or death.

2.2.2 Incidence

Less contemporary data is available overall for heart failure incidence. Extrapolation of the Framingham data suggested that there are around half a million new cases of heart failure per year in the US (American Heart Association, 2001; Ho *et al.*, 1993). Current analysis of the Framingham data suggest an incidence of around 10 per thousand after the age of 65 and that at the age of 40, the lifetime risk of developing heart failure is 1 in 5 for both men and women (Lloyd-Jones *et al.*, 2002). As with the prevalence estimates, there is a marked increase in the incidence of heart failure with age - <2 per 1000 patient years for those aged under 60 rising to 10 per 1000 patient years in the age group 70-79 and 25 per 1000 patient years for those aged over 80. The incidence is greater for men, but greater survival in females leads to approximately the same point prevalence for the sexes (Table 2.2).

A lower overall incidence was observed in the Rochester study during 1981 of 1.1 per 1000 patient years, with the same age and sex trends as the Framingham data (Rodeheffer *et al.*, 1993). More recently, in the UK, based on the numbers of patients proven to have heart failure following referral to a specialised heart failure clinic, the

Age	Male	Female
50-59	3	2
80-89	27	22

Table 2.2. Incidence of heart failure per 1000 patient years (Framingham data).

overall annual incidence was calculated as 1.85 per 1000 patient years (Cowie *et al.*, 1999). From American data, CHF incidence has not declined over the past 2 decades although overall survival has improved following disease onset (Roger *et al.*, 2004).

2.2.3 Heart failure hospitalisation

2.2.3.1 Admission trends

As with prevalence, incidence data will vary depending on the definition of heart failure, the study population and the era in which the data is gathered. As such, data pertaining to hospital admissions may be more useful in determining current trends. Heart failure is the most common primary diagnosis for those hospitalised over the age of 65 and some data exist for the trends in hospitalisation for heart failure in Europe, the USA and New Zealand over the last two decades (Doughty *et al.*, 1995; Ghali *et al.*, 1990; Gillum, 1993; Haldeman *et al.*, 1999; McMurray *et al.*, 1993b; Reitsma *et al.*, 1996; Rodriguez-Artalejo *et al.*, 1997; Ryden-Bergsten and Andersson, 1999). Admissions increase with age, are more commonly female patients than men and female patients tend to be older than male patients when admitted (Blackledge *et al.*, 2003). Figure 2.4 shows the general trend for increased rates of admission either as a primary or secondary diagnosis up until 1993 in developed countries.

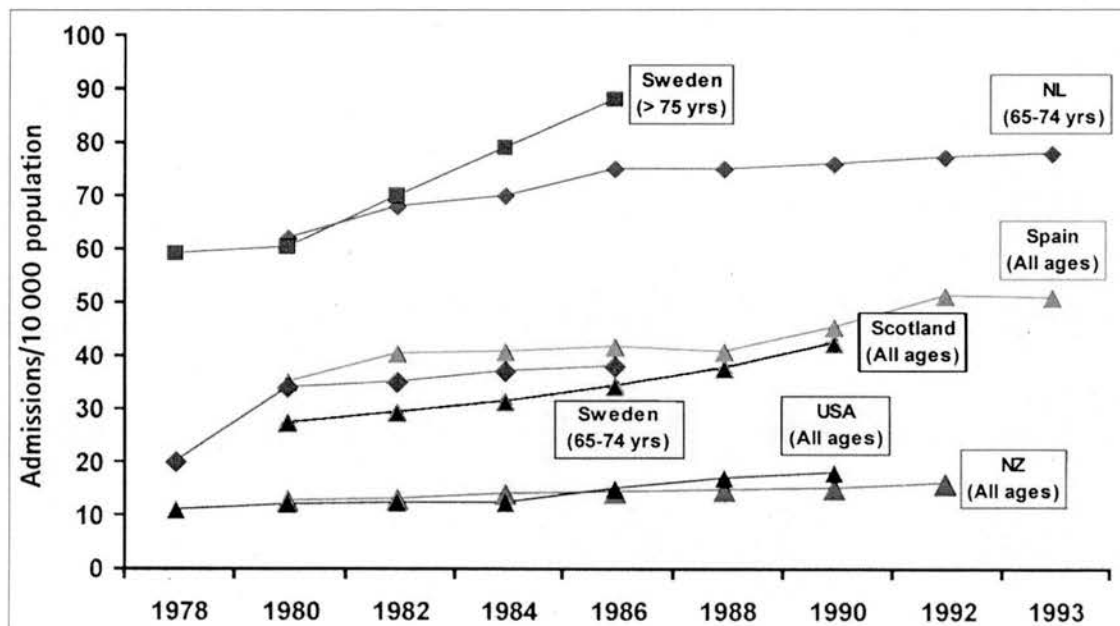


Figure 2.4. Heart failure admissions 1978-1993 per 10000 population at risk per annum. Adapted from (McMurray *et al.*, 1998).

However, there is some evidence that heart failure admissions may not be continuing to rise. Scottish data for the period 1980-1990 identified the number of hospitalisations with a principle diagnosis of heart failure rose from 1.3 to 2.12 per 1000 of the population, although it should be noted that these data are obtained from routine hospital discharge coding which may not be fully accurate. Subsequent data has shown an increase in admission rates, rising to a peak in 1993/1994 of 2.3 per 1000 for men and 2.4 for women (Stewart *et al.*, 2001b) but a lack of further increase beyond then. A similar trend, with admission rates reaching a plateau in the late 1990's was observed in a study from Leicestershire (Blackledge *et al.*, 2003). This is interesting and contrasts with the prediction of increased heart failure prevalence, but it may be linked to the observation that heart failure may now be less common in the post myocardial infarct group than previously, perhaps due to more widespread use of secondary prevention

therapy (Guidry *et al.*, 1999; Hellermann *et al.*, 2003). Alternatively, it may reflect better care of heart failure patients with more widespread use of ACE inhibitors and beta-blockers, or it may indeed reflect a change in the accuracy of diagnosis.

2.2.3.2 Seasonal Variations

My own experience in clinical practice would suggest that heart failure admissions occur more commonly in the winter months and in fact the seasonal variation in admission rates is well documented. For instance, in a recent Spanish study, hospitalisations were 25% above average in winter and 33% below average in the summer (Martinez-Selles *et al.*, 2002). This compares with other reports of seasonal variation in France (Boulay *et al.*, 1999) and the USA (Allegra *et al.*, 2001). A similar picture is seen in Scotland particularly in the elderly, with an associated seasonal variation in mortality (Stewart *et al.*, 2002b). This variation in admission rates could be explained by seasonal variations in blood pressure, cardiac arrhythmias and neurohormonal state secondary to temperature. Alternatively, it may be related to seasonal trends in rates of myocardial infarction or respiratory disease, particularly viral upper respiratory tract infections.

2.2.4 Mortality

Heart failure is a lethal condition and survival beyond 5 years is very poor.



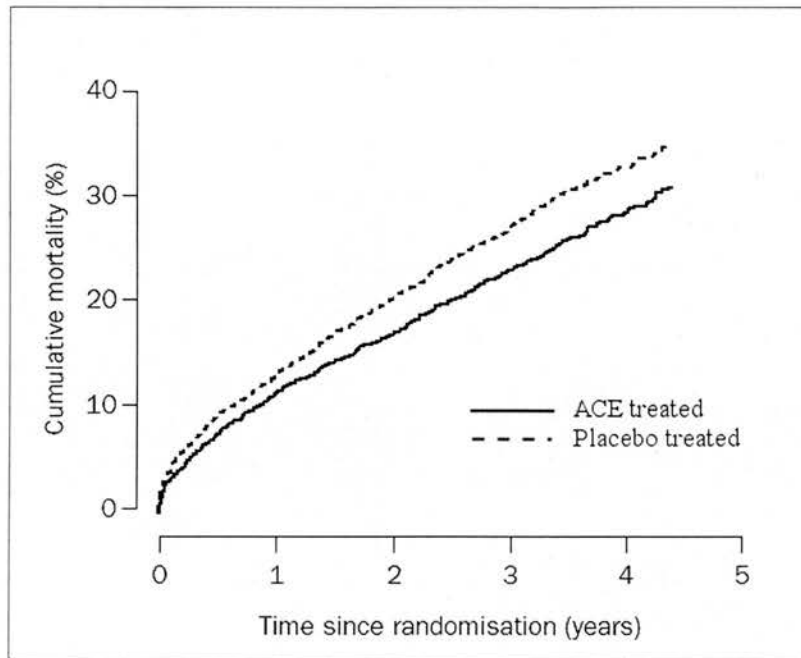


Figure 2.5. Cumulative mortality in a meta-analysis of trials of ACE-inhibitor therapy for patients with impaired left ventricular systolic function. Adapted from Flather *et al.* (2000).

Even in clinical trials this is demonstrated. For instance, Figure 2.5 shows the meta-analysis of mortality data for patients randomised to receive either placebo or an ACE inhibitor in five large clinical trials for subjects with reduced ejection fraction (the SAVE (Pfeffer *et al.*, 1992), AIRE (The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators, 1993) and TRACE (Kober *et al.*, 1995) trials of post myocardial infarction heart failure) combined with the data from the prevention and treatment components of the SOLVD study (SOLVD Investigators, 1991; SOLVD Investigators, 1992), most of whom had had a previous myocardial infarction (Flather *et al.*, 2000). Despite the young average age of the patients of 61 years and the likelihood of otherwise optimised medical therapy for hypertension and ischaemic heart disease, there is an overall mortality of around 30% at 4 years. Even in the CHARM study, a major clinical

trial performed in the era of modern pharmacological therapy for heart failure, and including relatively young patients with a mean age of 65 years, the all-cause mortality over 2 years in the placebo group was 21% and was 31% over 3.5 years (Young *et al.*, 2004). These disease populations do not reflect the true spectrum of heart failure in the community, however. From community prevalence and incidence studies discussed in sections 2.2.1 and 2.2.2, we know that the average age of the heart failure patient is older and at least half the patients are female – in the above meta-analysis of the ACE-inhibitor trials, however, only 19% were female (Flather *et al.*, 2000). As such, it is more realistic to look at data from community-based prospective observational studies.

For instance, a report from 4 decades of data from the Framingham cohorts (1950s – 1980s) identified 1 and 5 year survival rates of 57% and 25% for men and 64% and 38% for women, respectively (Kannel *et al.*, 1994). Increasing age was associated with a poorer prognosis. Little change was seen over these four decades despite improvements in treatment for coronary artery disease. The mortality rates above are notably high and, as a comparison, during the period 1979-1984, the 5-year survival rate from all cancers in the US was reported as 50% (Fraumeni *et al.*, 1989).

More recent data from the Rochester epidemiology project are similar. The same diagnostic criteria as the Framingham study were used and identified overall 1 and 5 year mortality rates of 28% and 66% in a cohort recruited in 1981, and 23% and 67% in a cohort recruited in 1991 (Senni *et al.*, 1999). As such, little change in mortality was seen over the period studied, perhaps indicating that ACE inhibitors were not being widely used in the community in the early to mid 1990s.

A recent analysis of the Framingham Heart Survey data suggests that 80% of men and 70% of women under the age of 65 with a diagnosis of heart failure will die within 8 years; the one year mortality rate is around 20% and the risk of sudden cardiac death is between 6 and 9 times higher than those without a diagnosis of CHF (Lloyd-Jones *et al.*, 2002).

Data from 1991 obtained from the Scottish Morbidity Record Scheme has identified a 5-year survival rate of 25%, poorer than most forms of cancer at that time, with lung cancer being the only malignancy with a poorer outcome (Stewart *et al.*, 2001a). Other Scottish crude survival data for those patients admitted to hospital between 1986 and 1995 are equally sobering (Table 2.3, MacIntyre *et al.*, 2000).

There is some evidence of improvement during the 1990's however. In Leicestershire, 1-year survival was estimated at 45% in 1993/1994 compared with 62% in 2000/2001, although this means that there is still about 40% mortality 1 year following an admission, which is still very poor (Blackledge *et al.*, 2003). Data from Scotland show a modest improvement in 1-year case fatality between 1986 and 1995 – from 46.7% to

Time from hospital admission	Case fatality rate
1 month	19.9%
1 year	44.5%
5 years	76.5%
10 years	87.6%

Table 2.3. Crude case fatality rates following hospitalisation in Scotland with a primary diagnosis of heart failure 1986 -1996.

42.4%, with an overall median survival increase from 1.23 years to 1.64 years (MacIntyre *et al.*, 2000). These data have been mirrored in other recent reports from developed countries and, again, absolute benefits in mortality are quite modest (Baker *et al.*, 2003; Feinglass *et al.*, 2003). These trends are positive but do represent small changes – the improved survival in Scotland quoted above for instance is only around 3 months overall. It is tempting to attribute these improved survival rates to improved drug treatment, particularly with ACE inhibitors and, more latterly, beta-blockers. However, admission thresholds and disease recognition may have changed over the last 10 years – as such, the mildly improved survival trends may simply represent the better survival in a group of patients with milder disease, or the increased likelihood of diagnosis of milder disease using modern techniques.

2.2.5 *Cost of heart failure*

Heart failure is a major public health problem and in a study from 1990 / 1991 it was estimated that heart failure was responsible for 1.2% of all NHS expenditure in the UK (McMurray *et al.*, 1993a). These costs were mirrored in other Western countries including the US where 1.5% of healthcare costs or 20 billion dollars was spent in 1999/2000 (American Heart Association, 1999).

Data for an analysis of costs incurred in both primary and secondary care for 1995 concluded that £716 million (1.8% of the total healthcare budget) in the UK was spent on heart failure, 69% of this being due to the cost of hospitalisation alone (around £½ billion). This high cost of institutionalisation in fact rises to £1.26 billion if the cost

nursing home care and admissions with heart failure listed as a secondary diagnosis are taken into account (Stewart *et al.*, 2002a). Although there is potential for polypharmacy in heart failure, drugs accounted for only 18% of costs in this study.

In the future, more expensive drug and device therapies will be introduced which will potentially increase expenditure. However, newer treatments are likely to reduce hospitalisation and may therefore prove to be cost effective. An alternative view is that newer therapies which reduce mortality will only serve to increase prevalence of the syndrome and may in fact increase the costs associated with drugs and out-patient care as more patients survive. Certainly, therapies which involve hospitalisation for initiation (i.e. placement of biventricular pacing devices) need to be carefully considered for their true cost effectiveness.

2.2.6 Future trends

Few formal projections exist for heart failure and vary considerably. In Scotland, hospitalisation is predicted to increase by 34% for males and by 12% for females by 2020 (Stewart *et al.*, 2003). In the Netherlands, incidence is expected to increase by 70% by 2010 (Bonneux *et al.*, 1994). Projections for Australia are similar (Kelly, 1997). Although these projections cannot account for the variation in prevalence of heart failure which may be occurring currently due to changes in incidence post MI, introduction of new therapies for heart failure and an increased awareness of the potential benefits of treatments in stages A and B of the syndrome which may favourably affect the clinical course of the syndrome, they do indicate a likelihood of an increased burden of heart

failure in the future.

2.2.7 *Summary and observations*

The above statistics are certainly troubling and despite the scope for error and variation generated by differing methodologies in data acquisition, there is no doubt that heart failure is common and is set to become even more so. There have been modest improvements in survival with the introduction of new therapies, in particular ACE inhibitors and beta-blockers, but the condition remains highly lethal. Costs associated with heart failure, predominantly due to hospitalisation, are set to rise and already consume a substantial proportion of the healthcare budget.

The epidemiology shows us that heart failure is a disease of the elderly and females account for more hospitalisations than men. Incidence of the disease is higher for men but the prevalence is approximately equal for both sexes owing to the greater longevity of women. Comorbidities are common in heart failure and are related to higher healthcare expenditure (Zhang *et al.*, 2003). What is striking, however, is how these demographics differ from those of the patients studied in clinical trials. Patients recruited in these large trials are generally younger, predominantly male and with few comorbidities. Medical therapy is usually optimally managed and this is reflected perhaps in the substantially lower mortality rates seen in the placebo arms of controlled trials when compared with the rates identified from population surveys. Despite this, survival is still relatively poor in these trials also.

Most published data relate to patients from Western nations. Limited epidemiological

data are available for the Indo-Asia region or for the developing world. In Hong Kong, incidence rates are similar to Western Europe and the US (Sanderson *et al.*, 1995) and is high in Africa (Oyoo and Ogola, 1999), South America (Mendez and Cowie, 2001) and Oman (Agarwal *et al.*, 2001). Aetiologies vary around the world. For instance, hypertensive heart failure is common in Nigeria (Rotimi *et al.*, 1998) and Chagas disease in South America (Mendez and Cowie, 2001), contrasting with the predominance of ischaemic heart disease as the most common aetiology in the Western world. However, there is a global epidemic of coronary artery disease and diabetes occurring, particularly involving the developing world and increased in part by the lifestyle changes associated with industrialisation and urbanisation (Yusuf *et al.*, 2001). Diabetes is common in the Indian subcontinent and it is troubling that very little data exist regarding therapeutic interventions in Chinese and Indian regions where approximately half of the world's population live.

These issues are of key importance in the specialised area of exercise training, a topic which will be discussed further in section 2.3.2. We know that heart failure patients are elderly and include at least equal numbers of females as males. We need to be sure that any intervention, particularly exercise training, is applicable to 'real' populations. A degree of motivation on behalf of the subject is required for exercise training and exercise is culturally acceptable in Western society. Few data exist for training in non-Caucasian populations and exercise is probably less acceptable culturally in these populations. Our understanding of the potential benefits of this particular treatment need to be viewed in a world-wide context.

2.2.8 Pathophysiology

The pathophysiology of heart failure is characterised by three things. Firstly, there is an initial insult impairing the heart's ability to fill with or eject blood, leading to a reduced ability to increase cardiac output as the body's metabolic needs increase. Secondly, there are a number of adaptive responses which act in the short term to maintain an appropriate cardiac output. Thirdly, over time, these adaptive changes result in detrimental changes which exacerbate symptoms and promote the progression of the syndrome and further reduction of cardiac reserve.

The adaptive and maladaptive responses will be discussed below, with particular emphasis on those changes which are responsible for exercise intolerance and which may be modified potentially by exercise training.

Although the majority of data on pathogenesis in heart failure relate to experimental work on systolic left ventricular dysfunction, the maladaptive changes equally apply to diastolic dysfunction as they occur in response to a reduction in the ability of the heart to maintain an appropriate cardiac output as metabolic demands increase.

2.2.8.1 Myocardial changes

The initial insult to the heart can be considered as a loss of functioning myocardium (e.g. infarction or coronary artery disease) or due to excessive overload (e.g. hypertension or valve disease). The development of the syndrome of heart failure occurs over time and it is useful to consider the process in separate stages. Of course, the process is a continuum rather than discrete stages with several mechanisms interacting. However, if one

considers the acute situation, as the ventricle fails, it is unable to eject a normal volume of blood during a single beat. As such, the volume at the end of systole (end systolic volume, ESV) is increased. Consequently, as the ventricle refills during diastole, a normal quantity of blood is added which then results in an increased volume in the ventricle at the end of diastole (increased end diastolic volume, EDV; movement from point A to B, Figure 2.6). This represents an increased preload for the subsequent beat and in accordance with the Frank-Starling mechanism, stroke volume (SV) increases for the next systole (Starling E.H., 1918). The increased contractility is due to sarcomere lengthening resulting in more optimal overlap and closer apposition of actin and myosin filaments, and increased Ca^{2+} sensitivity. Over time, the left ventricle may dilate and remodel, with the result that EDV is further increased. This increase in EDV occurs despite little change in EDP (movement from point A to C, Figure 2.6). Subsequent increases in EDP may then produce little change in diastolic volume, either due to ventricular stiffening or due to near maximal dilatation of the ventricle. As such, the failing heart is less able to use the Frank-Starling mechanism to maintain SV. This is diagrammatically represented in Figure 2.7 which shows the Frank-Starling curve for a normal heart, with large increases seen for relatively small changes in EDP but in heart failure a curve which is depressed and flattened, resulting in a relatively fixed stroke volume despite changes in EDP.

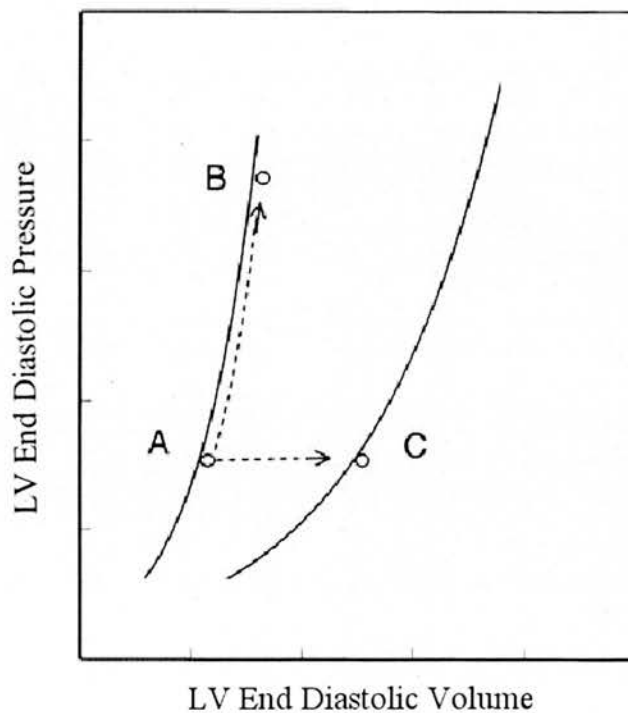


Figure 2.6. Relationship between left ventricular end diastolic volume and pressure in the failing heart.

As such, ventricular dilatation leads to initial compensation for reduced cardiac output but over time results in a blunting of the Frank-Starling mechanism. Left ventricular dilatation also results in further progression of the heart failure syndrome due to increased wall tension and over-stretch which requires greater energy expenditure for contraction and can result in diffuse myocyte apoptosis (Cheng *et al.*, 1995). Additionally, functional mitral regurgitation may develop, particularly during exertion thereby further reducing forward cardiac output.

Another important factor regarding the failing ventricle is also illustrated in Figure 2.7. SV in the failing ventricle is markedly affected by afterload and less affected by changes in preload in contrast to the healthy ventricle. This is important when considering other

maladaptive responses which will be discussed further below.

Cardiac output (CO), which is a function of stroke volume and heart rate, is reduced in heart failure both at rest and during exercise. Normally, CO increases during exercise due to a combination of increased heart rate and increased stroke volume, itself secondary to increased EDV and reduced ESV. In heart failure there is an attenuated ability to increase EDV due to ventricular stiffness or dilatation as described above, and a decreased ability to reduce ESV due to impaired contractility, decreased β -receptor responsiveness, increased systemic vascular resistance (secondary to increased sympathetic tone and activation of the renin-angiotensin system) and blunted arterial

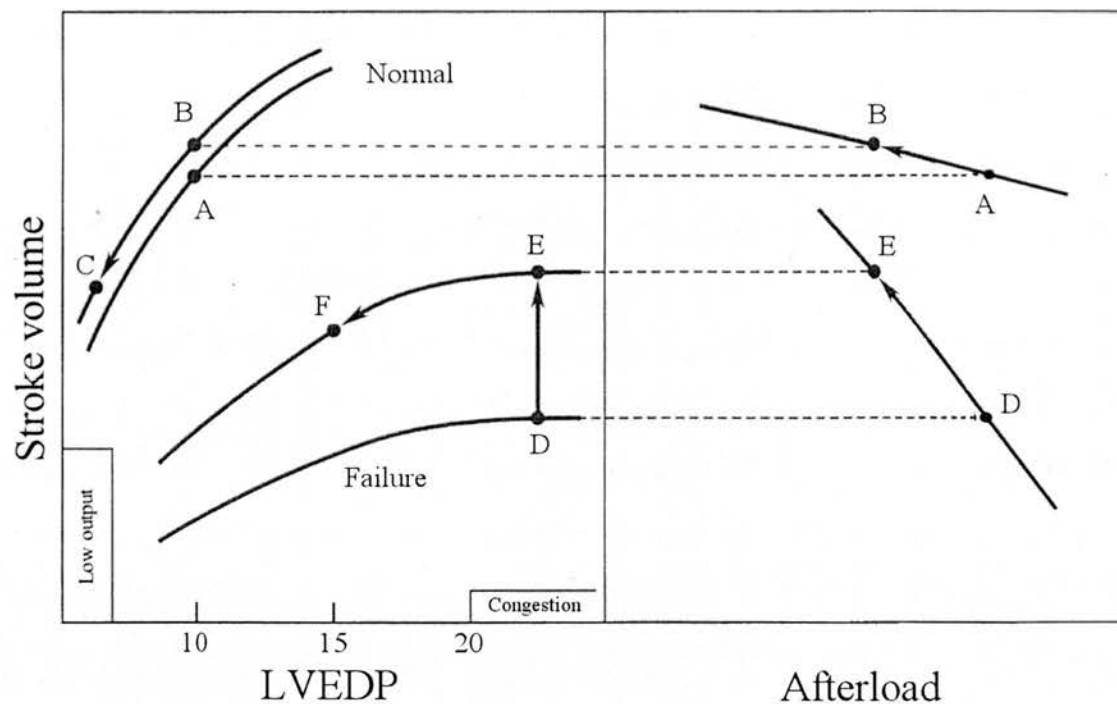


Figure 2.7. Frank-Starling mechanism in the normal and failing heart.

vasodilatory response to exercise (described below). As such, the heart relies more on an increase in heart rate to maintain an appropriate increase in cardiac output in heart failure during exertion. However, maximum heart rate is mildly decreased in heart failure and the heart rate reserve is markedly decreased owing to a higher resting heart rate, mostly due to the loss of parasympathetic vagal tone. This impairment of heart rate reserve is documented in heart failure and again, although initially beneficial, the resting tachycardia reduces the reserve available upon commencement of exertion.

The compensatory changes which occur in response to depressed cardiac function are protective and serve to increase cardiac output and hence tissue perfusion. In the chronic state they are deleterious, however, and result in progression of the syndrome, increased symptoms and organ damage.

2.2.8.2 Neurohormonal system

Vasoconstriction and salt/water retention are well recognised features of heart failure. Arterial hypoperfusion secondary to reduced cardiac output or systemic vascular resistance results in the activation of a number of reflexes which serve to retain salt and water. The reduction in perfusion may be sensed by mechanoreceptors in the left ventricle, carotid sinus, aortic arch and renal afferent arterioles with subsequent sympathetic activation, activation of the renal-angiotensin-aldosterone system, and release of arginine vasopressin. With the increase in circulating volume, filling pressure will increase which will serve to increase cardiac output (Schrier and Abraham, 1999). The counter-regulatory proteins atrial natriuretic peptide (ANP), brain natriuretic peptide

(BNP) and clearance natriuretic peptide (CNP) are also released, which enhance sodium excretion, aldosterone secretion and reduce sympathetic drive, systemic vascular resistance and right atrial pressure (Levin *et al.*, 1998). However, in more advanced heart failure, the vasoconstriction and salt/water retention of the neurohormonal responses predominate and form the basis for manipulation with modern pharmacological treatment.

2.2.8.2.1 Autonomic nervous system

There is an increase in sympathetic activity in heart failure which serves to maintain cardiac output acutely. Increased circulating levels of norepinephrine have been recognised for some time in heart failure (Chidsey *et al.*, 1962) and levels correlate with disease severity (Thomas and Marks, 1978). In the heart, catecholamines increase heart rate and myocardial contractility, and promote more rapid ventricular relaxation during diastole. Although individuals with severe end-stage heart failure may be dependent on the sympathetic drive for maintenance of cardiac output, there is no doubt that during the course of the syndrome, increased levels of norepinephrine are detrimental with toxicity to the myocardium (Mann *et al.*, 1992), promotion of arrhythmias and left ventricular hypertrophy and remodelling. Peripherally, arterial and venous vasoconstriction will serve to increase afterload and preload, respectively (Packer, 1992) and, as described earlier, increased afterload is detrimental in chronic heart failure. Additionally, as the syndrome progresses, there is decreased sensitivity of the heart to catecholamines and down-regulation of β -adrenoreceptors (Bristow *et al.*, 1982).

2.2.8.2.2 Renin-angiotensin-aldosterone system

Multiple mechanisms are responsible for the activation of this key system in chronic heart failure, the initial stage of which is renin release (Francis *et al.*, 1984). These mechanisms include sympathetic activity, hypoperfusion and delivery of hyponatraemic perfusate to the macula densa, diuretic use and low sodium diet, which both result in a relative reduction of circulating volume and also stimulate renin release. Renin is a proteolytic enzyme which promotes the cleavage of angiotensinogen to angiotensin I. Angiotensin converting enzyme (ACE) cleaves angiotensin I to form angiotensin II, which has a range of biological activities. Angiotensin II itself stimulates aldosterone release from the adrenal cortex which promotes sodium and water retention, and AVP release.

Angiotensin II acts primarily via the AT1 receptor resulting in arterial vasoconstriction, myocyte apoptosis, ventricular remodelling, polydipsia, norepinephrine release and sensitisation of blood vessels to norepinephrine.

Again, the initial activation of the system provides beneficial support in maintaining cardiac output and organ perfusion, but is detrimental in the long term.

2.2.8.2.3 Arginine Vasopressin

Arginine vasopressin (AVP) released from the hypothalamus or hypothalamoneurohypophyseal tract in response to activation of carotid baroreceptors during low circulatory pressure states reduces the excretion of water in the kidney at the collecting duct, again serving to increase circulatory volume. Normally, hyponatraemia would result in the discontinuation of AVP release but dysregulation of AVP occurs in the low pressure state of heart failure resulting in selective retention of water and

hyponatraemia. AVP is found in high levels in the circulation of hyponatraemic patients with heart failure (Szatalowicz *et al.*, 1981) and there is an ongoing assessment of the benefits of AVP blockade via vasopressin receptor antagonists. Additionally, AVP may contribute to myocardial dysfunction and increased vascular resistance promoting further progression of the syndrome.

2.2.8.2.4 Endothelin

Endothelin 1 (ET-1), the best characterised of the vascular endothelins and produced in response to external stimuli by vascular endothelial cells is a powerful vasoconstrictor and has emerged as a potentially important contributor to the syndrome of heart failure. Synthesis is enhanced by a number of factors associated with heart failure including angiotensin II, norepinephrine and hypoxia and elevated concentrations of ET-1 correlate with poorer clinical state (Kiowski *et al.*, 1995) and outcome (Pacher *et al.*, 1996). The bioactivity of ET-1 is mediated by 2 receptors – ET-A, found mainly in vascular smooth muscle and responsible for vasoconstriction and cell proliferation / hypertrophy, and ET-B, found predominantly on vascular endothelium and which mediates vasodilatation (Haynes and Webb, 1998).

2.2.8.2.5 Natriuretic peptides

This family of peptide hormones incorporates atrial or A-type natriuretic peptide (ANP), brain or B-type natriuretic peptide (BNP) and clearance natriuretic peptide (CNP). ANP and BNP have similar physiological actions including natriuresis, diuresis, vasodilatation, improved diastolic relaxation and reduced myocardial fibrosis. ANP acts as the predominant of the two circulating hormones in healthy individuals, is secreted in

response to atrial stretch and is more rapidly cleared than BNP. BNP is released by the ventricles in response to LV wall stress and dysfunction (Mukoyama *et al.*, 1991). This and BNP's longer half life results in BNP being the more useful biomarker in heart failure (Doust *et al.*, 2004). Both ANP and BNP are synthesised as larger pro-molecules with subsequent proteolytic cleavage into active and inactive fragments. The inactive N-terminal pro-BNP (NT-pro BNP) has a longer half-life than the active BNP and as such is often used in preference to BNP as a biological marker in research studies.

There is a close relationship between the degree of LV impairment and BNP (Richards *et al.*, 1993) and also NT-pro BNP (Hunt *et al.*, 1997). There is a clear association of BNP with symptoms of heart failure (Wieczorek *et al.*, 2002) and also with asymptomatic LV dysfunction (Mueller *et al.*, 2004).

BNP has been demonstrated to be useful as a highly specific aid to differentiate heart failure due to LV systolic impairment from other causes of breathlessness (Davis *et al.*, 1994; Maisel *et al.*, 2002) and, recently, NT-pro BNP has been shown to be perhaps more discriminating in this regard (Lainchbury *et al.*, 2003). BNP is also elevated in right ventricular impairment associated with pulmonary embolism (Kruger *et al.*, 2004) and primary pulmonary hypertension (Leuchte *et al.*, 2004), diastolic heart failure (Redfield *et al.*, 2004) and acute coronary syndromes (Wiviott *et al.*, 2004). BNP is also associated with worse prognosis (de Lemos *et al.*, 2003) and predictive of sudden cardiac death (Berger *et al.*, 2002). NT-pro BNP levels also predict worse outcomes and the need for more urgent cardiac transplantation (Gardner *et al.*, 2003; Richards *et al.*, 2001).

Importantly, BNP and NT-pro BNP can be used to monitor clinical progression in heart failure and these biomarkers have been used in clinical trials to assess outcome following an intervention. The converse is also true – NT-pro BNP guided therapy has been shown to be more effective than clinical monitoring in reducing cardiovascular events in heart failure patients (Troughton *et al.*, 2000). The longer half-life of NT-pro BNP and the availability of a rapid assay makes the use of this particular biomarker attractive both for study design and clinical management.

2.2.8.3 Peripheral changes

The central haemodynamic changes described in the preceding sections are only part of the pathophysiological change responsible for the generation of the syndrome of chronic heart failure. Abnormalities of ventilatory function, peripheral haemodynamics and skeletal muscle function have been identified and are key to the generation of symptoms in heart failure and perhaps also to disease progression. It is well recognised that ejection fraction in itself bears no relationship to peak exercise oxygen consumption (peak VO_2 ,

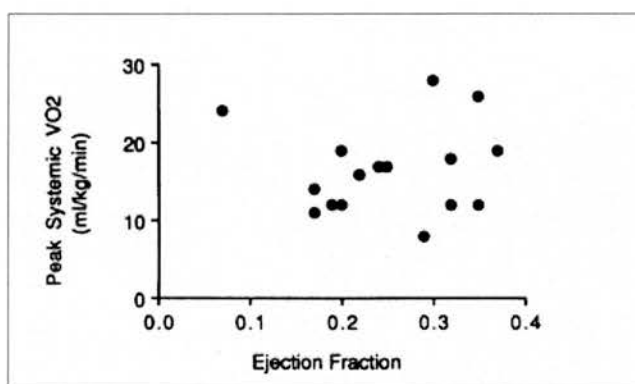


Figure 2.8. Relationship between ejection fraction and peak oxygen consumption. Adapted from (Minotti *et al.*, 1991).

Figure 2.8, Minotti *et al.*, 1991), the increment in ejection fraction during exercise does not relate to peak VO_2 (Higginbotham *et al.*, 1983; Szlachcic *et al.*, 1985) and that acute improvements in central haemodynamics do not result in rapid improvement in exercise capacity (Marzo *et al.*, 1993; Wilson *et al.*, 1984).

2.2.8.3.1 Skeletal muscle abnormalities

Decrease muscle strength and early fatigue are recognised in CHF and are in part due to muscle atrophy which may occur early in the course of disease progression (Buller *et al.*, 1991; Lipkin *et al.*, 1988; Mancini *et al.*, 1992). Although this may be due to disuse, other causative factors include the pro-inflammatory state observed in heart failure and abnormal skeletal muscle blood flow. Cytokines which promote a catabolic state are found in increased levels in heart failure, e.g., tumour necrosis factor α (TNF α), interleukin (IL) 2 and IL-6 (Adamopoulos *et al.*, 2002; Levine *et al.*, 1990; Marriott *et al.*, 1996). Decreased skeletal muscle blood flow observed in CHF patients (Zelis *et al.*, 1974) is unlikely to be directly due to the low cardiac output state during exercise in heart failure, again as acute changes in central haemodynamics following ACEi therapy (Drexler *et al.*, 1989) or transplantation (Sinoway *et al.*, 1988) do not result in immediate improvements in exercise capacity. The vascular endothelium regulates vasomotor tone and is recognised to be abnormal in CHF (Drexler *et al.*, 1992a). Endothelial function is closely involved in the control of tissue perfusion (Henderson, 1991) and dysfunction is associated with increased mortality (Fischer *et al.*, 2005; Katz *et al.*, 2005). Impaired vasodilatation secondary to endothelial dysfunction and the elevated concentration of peripheral vasoconstrictor neurohormones such as

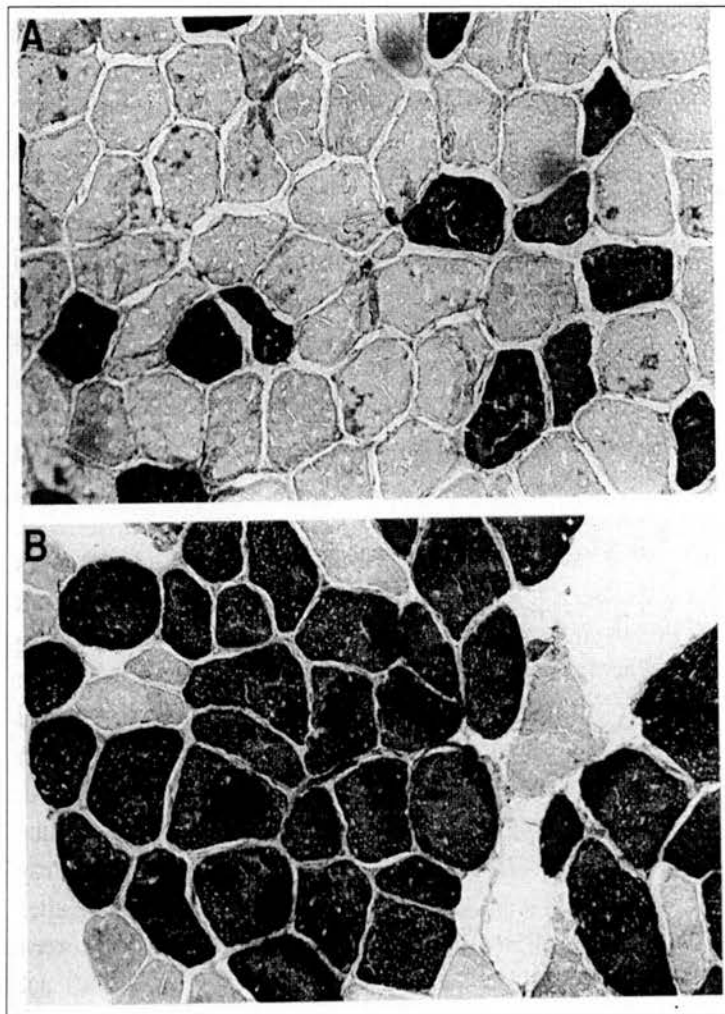


Figure 2.9. Muscle biopsy and myofibrillar ATPase stain. Light staining - type I fibre, dark staining - type II fibre, A - normal, B - CHF patient.

noradrenaline, renin, angiotensin II and vasopressin as described in section 2.2.8.2 is likely to play a significant contributory role.

Atrophy alone, however, is not the explanation for reduced muscle strength and early fatigue in CHF. There is a reduction in strength per unit muscle (Harrington *et al.*, 1997) which suggests qualitative changes also. Histologically, type I 'slow-twitch' muscle fibres are replaced by type IIb glycolytic fast twitch fibres which have a low capacity for

aerobic metabolism and hence may contribute to early fatigability (Drexler *et al.*, 1992b; Lipkin *et al.*, 1988). Figure 2.9 shows muscle biopsy specimens for normal and CHF patients stained for myosin ATPase with dark-stained type II muscle fibres over-represented in the CHF sample. Myosin heavy chain type I isoforms are reduced in CHF patients with reduction in proportion to decreased peak VO_2 (Sullivan *et al.*, 1997). At the ultrastructural and enzymatic level, mitochondrial volume density and surface density of cristae (associated with peak VO_2 at anaerobic threshold) are reduced (Drexler *et al.*, 1989) along with oxidative mitochondrial enzyme activity (reduced cytochrome oxidase, citrate synthase and succinate dehydrogenase, Sullivan *et al.*, 1990). These changes place more reliance on anaerobic metabolism in the skeletal muscle of CHF patients and help explain the early fatigue and early lactate production they experience (Weber and Janicki, 1985).

2.2.8.3.2 Ventilatory abnormalities

Breathlessness is a common symptom in CHF. For a given level of exercise, ventilation is abnormally increased and this is demonstrated by the abnormal relationship of ventilatory equivalent (VE) to CO_2 production (VCO_2), i.e., VE/VCO_2 slope (Fink *et al.*, 1986; Sullivan *et al.*, 1988b). The VE/VCO_2 slope is increased in heart failure and has been demonstrated to be an independent predictor of mortality and closely associated with disease severity (Corra *et al.*, 2002; Guazzi *et al.*, 2003). VCO_2 itself is not thought to drive ventilation during exercise, but rather that VCO_2 is driven by VE and that there is a non-pulmonary ventilatory stimulus (Franciosa *et al.*, 1984; Rubin *et al.*, 1982). The small afferent ergoreceptors found in skeletal muscle are sensitive to the type of

metabolic changes observed in CHF and their activity is enhanced compared to control subjects (Piepoli *et al.*, 1996; Ponikowski *et al.*, 2001; Scott *et al.*, 2002). Ergoreceptor activation results in an exaggerated sympathetic and ventilatory response to exercise and may therefore be a link between metabolic peripheral muscular changes and exertional breathlessness.

2.3 Therapy

2.3.1 Pharmacological and device therapy

There is an overwhelming evidence base for pharmacological treatment in heart failure and an emerging evidence base for device therapy, i.e., cardiac resynchronisation therapy with or without automated defibrillator function. These therapies do not directly relate to the trials performed during the course of my research and will not be discussed further. Position statements and guidelines from the European Society of Cardiology and American College of Cardiology / American Heart Association have been published and review the evidence (Hunt *et al.*, 2005; Nieminen *et al.*, 2005).

2.3.2 Exercise training

Historically, it was believed that exercise therapy was detrimental in CHF and until the late 1970's / early 1980's it was not encouraged. Uncontrolled studies around that time suggested exercise tolerance could be improved by training (Conn *et al.*, 1982; Lee *et al.*, 1979; Letac *et al.*, 1977) although conflicting outcomes were described during the 1980's with respect to LV remodelling post-anterior myocardial infarction following

low-intensity training (Jugdutt *et al.*, 1988). Since then, many studies have been performed looking at every known aspect of pathological change in CHF and have largely demonstrated benefit following training and this has led to the adoption of training in the current guidelines for CHF management (Hunt *et al.*, 2001; Remme and Swedberg, 2002; Scottish Intercollegiate Guidelines Network, 2002; Working Group on Cardiac Rehabilitation & Exercise Physiology and Working Group on Heart Failure of the European Society of Cardiology, 2001). A review of some of the influential studies performed during the last 2 decades which have demonstrated improvements following training is given below.

2.3.2.1 Central haemodynamics

Although the majority of benefit from training is likely to be due to peripheral adaptations, improvement in central haemodynamic variables has been observed. There is minimal or no change in ejection fraction following training (Belardinelli *et al.*, 1995a; Belardinelli *et al.*, 1998b; Sullivan *et al.*, 1988a) but small improvements in cardiac output are observed during exercise following a period of training (Belardinelli *et al.*, 1995b; Dubach *et al.*, 1997b; Dubach *et al.*, 1997a; Hambrecht *et al.*, 1995). This small increase in cardiac output can be attributed to a small increase in maximal heart rate (around 4-8%) and small increases in stroke volume coupled with a small reduction in systemic vascular resistance. One study has shown an improvement in the diastolic filling rate following training with improvements correlating with increased cardiac index at peak exercise (Belardinelli *et al.*, 1996). There is no evidence of significant ventricular remodelling following exercise training (Dubach *et al.*, 1997b; Giannuzzi *et*

al., 1993; Jette *et al.*, 1991; Klecha *et al.*, 2007; Myers *et al.*, 2000a), and in fact one study has suggested an adverse effect on remodelling post MI following training (Jugdutt *et al.*, 1988). There may be some improvement in perfusion and contractility following training as assessed following a short period of training by dobutamine stress echocardiography and thallium perfusion scintigraphy (Belardinelli *et al.*, 1998a) where an approximately 30% improvement in contractility and thallium uptake was observed. This contrasts with other studies where LV contractility at rest and during exercise was unchanged following training (Dubach *et al.*, 1997b; Giannuzzi *et al.*, 1997; Giannuzzi *et al.*, 1993).

2.3.2.2 Neuroendocrine function

Results from studies measuring catecholamine spill-over are inconsistent with some studies showing reduced noradrenaline levels following training (Coats *et al.*, 1992; Hambrecht *et al.*, 1995; Tyni-Lenne *et al.*, 2001), but not others (Kiilavuori *et al.*, 1999). Improvement in heart rate variability and reduction in resting heart rate which indicate reduced sympathetic drive and increased vagal tone have also been demonstrated following training (Coats *et al.*, 1992; Larsen *et al.*, 2004).

2.3.2.3 Endothelial function

Improvement in oxygen delivery and extraction by improved peripheral circulation has been proposed as a mechanism for improved exercise capacity following training. Leg blood flow has been seen to increase following 4-6 months of exercise training with improvement in oxygen extraction peripherally and reduced lactate formation at

submaximal exercise (Sullivan *et al.*, 1988a). Additionally, peak leg blood flow response has been shown to improve following training with reduced leg vascular resistance at submaximal and peak exercise (Hambrecht *et al.*, 1995). To explore this further, a number of studies have investigated the effect of training on the vascular endothelium. Endothelial dependent relaxation of upper-limb vessels in response to flow is improved following upper limb exercise in CHF patients (Hornig *et al.*, 1996) and lower limb training improves leg blood flow via endothelial-dependent vasodilatation with improvements correlating with increases in peak VO_2 (Hambrecht *et al.*, 1998). Improvement in epicardial endothelial dysfunction has also been demonstrated in one small study following a short period of exercise training (Hambrecht *et al.*, 2000b).

2.3.2.4 Exercise capacity and cardiopulmonary data

Peak oxygen consumption (peak VO_2) during exercise is a reliable indicator of exercise capacity in heart failure and is closely associated with prognosis (Myers *et al.*, 2000b). Allowing for methodological differences between studies examining effects of exercise in heart failure, specifically mode and duration of training, many studies demonstrate clear improvement in peak VO_2 , with increases between 12% and 31% (Table 2.4). Some uncertainty exists regarding the required duration of training, but it is likely that continued training is required to maintain benefit (Meyer *et al.*, 1996; Tenenbaum *et al.*, 2006) and that supervision may be required (McKelvie *et al.*, 2002).

It is possible that aetiology of heart failure is important in determining response to training with one study suggesting greater benefit for patients with non-ischaemic heart

failure (Keteyian *et al.*, 1996) although ischaemic patients with evidence of hibernating myocardium on dobutamine stress echocardiography may benefit most (Belardinelli *et al.*, 1998b).

Submaximal exercise parameters are commonly assessed in exercise training studies also, including 6-minute walk distance (6MW) and exercise duration. Improvements in 6MW distance have consistently been seen in trained subjects e.g., (Freimark *et al.*,

Authors Reference	No. of Patients	Exercise Programme		%VO ₂ Increase (trained vs. control patients)
		Duration, wk	Mode of training	
Jette, <i>et al.</i> (1991)	18	4	Mon–Fri. am: Jog at 70% to 80% max HR for 5 min 3x/wk; calisthenics 30 min; cycle 15 min at 70% to 80% max HR. pm: Walk 30 to 60 min.	22 in group with EF <30%
Belardinelli, <i>et al.</i> (1992)	20	8	Cycle at 40% peak VO ₂ 3x/wk.	20
Coats, <i>et al.</i> (1992)	17	8	Cycle 20 min at 60% to 80% max HR 3x/wk.	18
Belardinelli, <i>et al.</i> (1995a)	55	8	Cycle 40 min at 60% VO ₂ max 3x/wk.	12
Hambrecht, <i>et al.</i> (1995)	22	3	Walk 10 min 6x/d at 70% VO ₂ max 2x/wk.	31
Keteyian, <i>et al.</i> (1996)	29	24	Rating of perceived exertion, 12–14. Treadmill, cycle, rowing, and arm ergometer at 60% exercise capacity for 33 min 3x/wk.	16.3
Radaelli, <i>et al.</i> (1996)	6	5	Cycle 20 min 5 d/wk.	15
Dubach, <i>et al.</i> (1997b)	25	4	Walk 60 min 2x/d; cycle 40 min 4x/wk at 80% VO ₂ max.	26
Tyni-Lenne, <i>et al.</i> (1997a)	16	8	Knee extensor: 60 repeats/min for 15 min for 8 wk (at 65% peak work rate for 4 wk and then 75% peak work rate for 4 wk).	14
Callaerts-Vegh, <i>et al.</i> (1998)	17	8	Walk 1 h, 2x/d; cycle 45 min at 70% to 80% HR reserve 4x/wk.	30.9
Reinhart, <i>et al.</i> (1998)	25	8	Cycle 40 min at 70% to 80% max capacity 4x/wk; walk 1 hour 2x/d.	29
Belardinelli, <i>et al.</i> (1999)	99	8 (plus maintenance)	Cycle at 60% peak VO ₂ 3x/wk for 8 wk. Maintenance: 2x/wk for 12 mo.	18 at 2 mo; 23 at 14 mo
Taylor (1999)	8	8	Train 30 min at 45% to 70% peak VO ₂ 3x/wk.	17.6
Sturm, <i>et al.</i> (1999)	26	12 (plus maintenance)	Step aerobics and cycle at 50% capacity for 12 wk; then step aerobics 100 min/wk and cycle 50 min/wk.	23.3
Keteyian, <i>et al.</i> (1999)	43	24	Treadmill, cycle, and arm ergometer at 60% to 80% max HR for 33 min 3x/wk.	14.3

Table 2.4. Effects of exercise training on VO₂ in CHF patients.

2007; McKelvie *et al.*, 2002) as have improvements in exercise duration (Wielenga *et al.*, 1999). The usefulness of the 6MW test as a submaximal marker of exercise capacity is discussed further in section 3.3.2.

Another submaximal exercise parameter is the anaerobic threshold (AT) measured during cardiopulmonary exercise testing. The terms anaerobic threshold, ventilatory threshold and lactate threshold are often used interchangeably in the literature although the processes they describe are subtly different; the AT, however, does relate to the point where there is a sustained switch to predominantly anaerobic metabolism during exercise. The measurement and interpretation of AT during cardiopulmonary exercise testing differs between studies and is discussed further in section 3.3.4.3. Low VO_2 at AT is associated with poorer outcome (Gitt *et al.*, 2002) and exercise training has been shown to significantly increase VO_2 at AT (Hambrecht *et al.*, 1995; Wielenga *et al.*, 1999). Alternatively, the lactate threshold can be measured directly with venous blood sampling during incremental exercise testing and VO_2 at lactate threshold has been shown to improve following training (Belardinelli *et al.*, 1992; Dubach *et al.*, 1997a); venous lactate concentrations were lower in one study for trained subjects during submaximal exercise testing, indicating delayed progression to anaerobic metabolism (Hambrecht *et al.*, 1995).

Ventilatory abnormalities indicated by the exaggerated VE/VCO_2 slope (discussed in section 3.3.4.4) are improved following training (Coats *et al.*, 1992; Guazzi *et al.*, 2004). Mechanisms are likely to relate to improved skeletal muscle characteristics and delayed onset of lactate accumulation, although enhanced ventilation / perfusion matching and

reduced ergoreceptor activation have been proposed (Clark *et al.*, 1996; Mancini *et al.*, 1995; Piepoli *et al.*, 1996). The effectiveness of specific respiratory muscle training has also been examined and maximal ventilatory capacity and inspiratory / expiratory muscle strength improve with targeted respiratory training (Mancini *et al.*, 1995).

2.3.2.5 Skeletal muscle

The abnormalities in skeletal muscle function described in section 2.2.8.3.1 can be at least partially reversed by training. Belardinelli, *et al.* demonstrated increased cross sectional area of both type I and type II fibres following an 8-week training programme (Belardinelli *et al.*, 1995b). The fibre-type switch was reversed following a longer period of training which may improve the early fatigue of CHF patients during exercise (Hambrecht *et al.*, 1997).

Beneficial changes in oxidative capacity have also been observed following training. Belardinelli, *et al.* observed a 22% increase in volume density of mitochondria following training, which was correlated to peak VO_2 ($r = 0.77$, $p < 0.0002$) and lactate threshold ($r = 0.81$, $p < 0.0001$, Belardinelli *et al.*, 1995b). The mitochondrial total volume density and volume density of cytochrome c oxidase-positive mitochondria increased significantly, whereas volume density of cytochrome c oxidase-negative mitochondria remained unchanged following training with increased oxidative capacity highly correlated with improvement in peak VO_2 (Hambrecht *et al.*, 1995; Hambrecht *et al.*, 1997). Additionally, Hambrecht, *et al.* (1997) demonstrated a 92% increase in surface density of mitochondrial inner border membrane and an increase in the surface density

of cytochrome c oxidase-positive mitochondrial cristae.

Early reliance on anaerobic metabolism can be assessed by ^{31}P -MRI scanning to measure phosphocreatinine depletion. It has been shown that training results in a reduced depletion of phosphocreatinine during exercise and an accelerated recovery of phosphocreatinine following exercise, indicating less reliance on anaerobic metabolism during exercise and an increased rate of mitochondrial ATP synthesis (Adamopoulos *et al.*, 1993). Minotti, *et al.* demonstrated that there was a two- to three-fold increase in endurance following training associated with a slower increase in inorganic phosphate (Pi) and decline in phosphocreatine (PCr) and a beneficial change in the Pi/PCr ratio to workload regression slope, implying improved oxidative metabolism (Minotti *et al.*, 1990).

Catabolism induced by pro-inflammatory cytokines is a possible mechanism for skeletal muscle atrophy in heart failure and an attenuated pro-inflammatory state following training has been demonstrated (Adamopoulos *et al.*, 2002).

2.3.2.6 Quality of life

Not all training studies address quality of life and those that do vary in methodology and results. Table 2.5 summarises trial data and methodology for those studies that have reported on quality of life outcomes. The optimal quality of life assessment tool is uncertain at present and some studies have used multiple assessment tools. The majority of the studies listed in Table 2.5 do show a positive effect for quality of life although some others showed no benefit (Cider *et al.*, 1997; Johnson *et al.*, 1998; Owen and

Croucher, 2000). It is not surprising that short-term quality of life scores improve following short-term training regimes in unblinded trials and the long term effects on quality of life following training still requires evaluation, although the results from Belardinelli, *et al.* (1999) are encouraging, suggesting a sustained improvement in quality of life at follow-up.

2.3.2.7 Morbidity and mortality

Exercise training studies have tended to enrol only small numbers of patients and, as

Author	Interval	Assessment tool	Outcome
Belardinelli, <i>et al.</i> (1999)	Baseline, 2, 14, 26 months	MLWHF	Positive at 2 months, stable thereafter
Cider, <i>et al.</i> (1997)	Baseline, 20 weeks	NHP, QLQ-HF	NHP: positive in control group. QLQ-HF – no change
Coats, <i>et al.</i> (1992)	8 weeks crossover	Likert scale	Positive
Johnson, <i>et al.</i> (1998)	Baseline, 8 weeks	CHFQ	No change
Kavanagh, <i>et al.</i> (1996)	Baseline, 16, 26, 52 weeks	CHFQ, SG	Trend for improvement
Koch, <i>et al.</i> (1992)	Baseline, 12 weeks	Visual scale	Uncertain - no statistics reported
Oka, <i>et al.</i> (2000)	Baseline, 12 weeks	CHFQ	Positive
Owen and Croucher (2000)	Baseline, 12, 26 weeks	MLWHF	No change
Quittan, <i>et al.</i> (1999b)	Baseline, 12 weeks	SF-36	Positive
Shephard, <i>et al.</i> (1998)	Baseline, 16 weeks	CHFQ, SG	Positive
Tyni-Lenne, <i>et al.</i> (1996)	Baseline, 8 weeks	SIP, SOC	SIP – positive, SOC – no change
Tyni-Lenne, <i>et al.</i> (1998)	Baseline, 8 weeks	SIP, SOC	Positive
Tyni-Lenne, <i>et al.</i> (1997b)	Baseline, 8, 16 weeks	SIP, SOC	SIP – positive, SOC – no change
Tyni-Lenne, <i>et al.</i> (1999)	Baseline, 8 weeks	SIP, SOC, MLWHF	MLWHF – positive. SIP, SOC – no change
Wielenga, <i>et al.</i> (1999)	Baseline, 12 weeks	HPPQ, SAGWB	SAGWB – positive. HPPQ – trend only.
Willenheimer, <i>et al.</i> (1998)	Baseline, 16 weeks	DFI, Global QoL, PAS	Positive

Table 2.5. Quality of life outcomes following CHF exercise training trials.

such, event rates are low. The studies have not, therefore, been adequately powered to assess hospitalisation rates and mortality data. The older studies predate the widespread use of cardioselective beta-blocker therapy and this makes interpretation of morbidity / mortality data harder. The EXERT trial randomised 181 patients to usual care or 3 months of supervised exercise training followed by 9 months of home-based exercise training (McKelvie *et al.*, 2002). After 3 months, a 10% increase in peak VO_2 was observed, rising to 14% after 12 months. However, adherence to training was poorer during the home-based phase of the trial and there was no observed difference in hospitalisation or mortality. This contrasts with Belardinelli, *et al.* (1999) which showed a significantly lower combined end-point of hospitalisation and cardiac mortality (5 vs. 14 events, RR 0.29, $p=0.02$) and a separation of survival curves (9 vs. 20 events, RR 0.37, $p=0.01$) between trained and non-trained groups beyond 1 year. The issues of population selection which will be explored further in chapter 8 may be of relevance with respect to the disparity in results of these two trials.

Smart and Marwick have performed a meta-analysis of 81 trials of exercise training in heart failure (Smart and Marwick, 2004). This encompassed 2387 patients and over 60 000 hours of training in total. 26 patients randomised to exercise group and 41 randomised to non-exercising groups died (OR 0.71 95% CI 0.37 to 1.02, $p = 0.06$). The combined end-point of death or adverse event including hospitalisation rate was 56 in the exercising groups and 75 in the control groups (OR 0.98, 95% CI 0.61 to 1.32, $p = 0.60$). As such, there is a suggestion of mortality benefit following training, but the evidence is not concrete.

A further meta-analysis of selected exercise training trials has also been reported (Piepoli *et al.*, 2004). This used individual patient data from 9 randomised parallel group controlled trials with an exercise duration of at least 8 weeks and a follow-up period of between 159 and 2284 days. Between 27 and 181 patients were participating in the individual trials and a total of 801 patients' data-sets were analysed, 395 of whom had been randomised to an exercise programme. 88 deaths were observed in the exercising arm and 105 in the control arm (HR 0.65, 95% CI 0.46 – 0.92, $p=0.015$). The secondary endpoint of death or hospital admission was also significantly lower in the exercising arm (127 vs. 173 events, HR 0.72, 95% CI 0.56 – 0.93, $p=0.011$). Strictly speaking, this was not a true meta-analysis as data were pooled and treated as a single study, potentially introducing bias and over-precision. Additionally cox-regression was used to correct for the individual trials which will potentially bias for the study with the longest period of follow-up (Belardinelli *et al.*, 1999) which had a large observed mortality difference between trained and non-trained groups.

These data require confirmation in a larger trial before firm conclusions regarding the potential mortality benefit with training can be drawn. HF-ACTION is a large study which is currently underway and will attempt to address this question (Bensimhon *et al.*, 2007). This trial aims to recruit 3000 NYHA class II to IV CHF patients with an average follow-up period of 2.5 years. The applicability of trial data to the wider CHF population derived from this type of study is also a matter of debate in view of potential differences between trial and general CHF populations. Despite this, there is an indication that exercise training may confer a mortality benefit, which is an attractive prospect, and hopefully we will have a better understanding of this when HF-ACTION reports.

2.4 Rationale for studies in this thesis

2.4.1 Study 1. *A randomised study of home-based neuromuscular stimulation of the legs and conventional bicycle exercise training for patients with chronic heart failure.*

This trial was conceived at the time that recommendations for management of chronic heart failure had been published (Hunt *et al.*, 2001; Remme and Swedberg, 2002; Scottish Intercollegiate Guidelines Network, 2002; Working Group on Cardiac Rehabilitation & Exercise Physiology and Working Group on Heart Failure of the European Society of Cardiology, 2001). Exercise training / rehabilitation was included in the recommendations but it is widely appreciated that the heart failure patient is both detrained and often demotivated. As such, delivery of this therapy is difficult. Neuromuscular electrical stimulation (NMS) of limbs has been shown to be effective in the rehabilitation for patients detrained due to other conditions such as stroke disease. Additionally, neuromuscular stimulators have become popular with healthy individuals attempting to increase muscle performance / bulk either in addition to or instead of conventional training in the gym. These units are commercially available for little cost and are frequently advertised as a way of achieving improved performance with less effort. Study 1 is the pilot study intended to explore the concept that these devices can be used for CHF patients. The study is randomised for conventional bicycle training against NMS training of quadriceps and gastrocnemius muscles but does not use a control population. Patients exercise for six weeks using either conventional or NMS training

with functional performance assessments before and after the training period. The main aim of this study is to explore the effectiveness and safety of NMS training at home. Issues such as motivation and compliance are also discussed.

2.4.2 Study 2. Maximum oxygen uptake corrected for skeletal muscle mass accurately predicts functional improvements following exercise training in chronic heart failure.

This study was designed to explore the effect of exercise training using NMS on skeletal muscle in CHF patients. Dual energy X-ray absorptiometry (DEXA) can accurately measure lean body mass and we proposed that small changes in skeletal muscle mass following a period of training might be detectable using this technique. Alternatively, qualitative changes in skeletal muscle following training have been demonstrated previously (Adamopoulos *et al.*, 1993) and the contribution of qualitative and quantitative adaptations following exercise in CHF patients is as yet unknown. By performing DEXA scanning before and after conventional and NMS training, we aimed to explore this relationship. Finally, it is well recognised that lower muscle mass is associated with a worse outcome in heart failure (Anker *et al.*, 1997b; Anker *et al.*, 2003). Reversal of this cachectic state may improve prognosis. Identifying whether patients with the lowest muscle mass prior to training experience the same or different degrees of benefit from training with respect to exercise performance or muscle mass as patients with higher baseline muscle mass or exercise capacity may have implications in the selection of patients for rehabilitation and training in the future. It is as yet unclear

whether patients with poorer baseline function have as much to gain from training as their fitter counterparts.

2.4.3 Study 3. Change in circulating cytokines following two forms of exercise training in chronic stable heart failure.

It is well recognised that a pro-inflammatory state exists in CHF patients and that the degree to which this is present is associated with disease severity (Levine *et al.*, 1990; Torre-Amione *et al.*, 1996a). The third study was designed to explore the association between disease severity / exercise performance and markers of inflammation before and after a period of training. Different training regimes may have differing effects on the pro-inflammatory state which have not yet been identified. The study compares NMS and conventional training with respect to high sensitivity C-reactive protein (hs-CRP), interleukin 6 (IL-6), tumour necrosis factor alpha (TNF α) and the two soluble TNF α receptors, sTNF $_{r1}$ and sTNF $_{r2}$. Patients exercise for 6 weeks using either conventional or NMS training with functional capacity assessments and cytokine assays at the beginning and the end of the training period.

2.4.4 Study 4. Neuromuscular and conventional exercise training in stable and recently decompensated patients with chronic heart failure.

This study expands on the concepts explored in chapter 4 (study 1). Exercise training, either conventionally performed or using NMS in CHF patients is studied, on this occasion with the addition of a control CHF population to aid the interpretation of

findings. Furthermore, in view of the fact that patients participating in studies, particularly those involving exercise training, appear highly selected for their stability and greater baseline fitness, this study includes patients who have recently been admitted to hospital following an episode of decompensated heart failure. By including this group, this study is designed to explore the hypothesis that early rehabilitation of patients with recently decompensated symptoms is as safe and as effective as exercise training in stable patients. The inclusion of these patients is challenging from a methodological point of view and issues regarding drop-out from the study and patient compliance are discussed. Patients are randomised to either control (no exercise), conventional or NMS training regimes for 6 weeks with functional capacity assessments and NT-pro BNP assay before and after the study period. A further assessment of functional capacity is made after a further 6 weeks of detraining.

2.4.5 Study 5. Participants suitable for inclusion in exercise training trials are substantially different from the general heart failure population.

Whilst study 4 had included a broader range of patients compared with other exercise training trials in the literature, it is still apparent that many patients seen in hospital, either in clinic or on the wards, are not eligible to participate in such trials based on standard inclusion and exclusion criteria. Certain patients with orthopaedic, neurological or simply severe heart failure symptoms who are unable to perform the necessary performance assessments in clinical trials are automatically excluded from such studies. Despite this, it is possible that they have much to gain from training, particularly regimes which require less physical effort and / or less motivation to perform. As such,

study 5 examines the characteristics of patients willing and able to participate in an exercise training study and compares them to the population of heart failure patients from which they are recruited. A comparison is also made between the characteristics of stable patients, traditionally included in CHF exercise studies, recently decompensated patients, i.e., those recently discharged following a hospital admission due to decompensated heart failure, and patients examined as part of the ExTraMATCH collaborative summary, a meta-analysis of several well-designed and frequently cited CHF exercise training trials. No such data is yet available in the literature regarding this subject.

The studies were carried out between 1999 and 2004. Scientific research is often collaborative and multiple investigators are often involved in the prosecution of clinical trials. Only the pilot study (study 1) involved significant collaboration with another investigator. Dr S. Harris commenced this pilot trial collecting approximately 50% of the data between 1999 and 2001. The remainder of the data collection for this and the other four studies, along with all data analysis and manuscript preparation is my own work, with the support of Ms S McKee, heart failure research nurse and under the guidance of the two project supervisors, Professor KAA Fox and Dr MA Denvir. The research was carried out at the Western General Hospital, Edinburgh and, latterly, at the Wellcome Trust Clinical Research Facility at the Western General Hospital. The studies were supported financially with project grants from the British Heart Foundation.

3 Methods

3.1 Patient selection

3.1.1 *Studies 1-3*

Patients included in studies 1-3 were recruited from hospital out-patient clinics and were classed as having stable chronic heart failure (S-CHF). This was defined as having been diagnosed in the past with heart failure on the basis of symptoms of breathlessness and exercise intolerance and impaired left ventricular systolic function with a calculated ejection fraction of less than 40% using the modified Simpson biplane method. At the time of recruitment, patients described NYHA class II or III symptoms. Stability was defined as no alterations in medical therapy within one month and no myocardial infarction within three months prior to inclusion. No weight loss of greater than 6% was reported for any of the patients in the preceding 6 months. All patients were on appropriate medical therapy including angiotensin converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB), loop diuretics, aldosterone antagonists, digoxin and beta-blockers. None of the subjects was participating in an exercise programme prior to inclusion in the studies. Patients were excluded if they had co-existing respiratory, neurological, orthopaedic or peripheral vascular disease that would prevent either a bicycle exercise training programme or completion of the exercise performance assessments throughout the course of the studies. None of the subjects taking part in the study was known to have any intercurrent infective or malignant disease.

For study 2, an additional 20 healthy age-matched control subjects with no prior history of cardiac or any other chronic illness were recruited from within the department and were used as a comparison group.

3.1.2 Studies 4,5

Stable patients (S-CHF) for studies 4 and 5 were recruited and defined in the same way as for studies 1-3 (section 3.1.1). Recently decompensated patients (RD-CHF) were also recruited. All RD-CHF subjects with potential for inclusion had been previously diagnosed with heart failure on the basis of clinical assessment and documented left ventricular systolic dysfunction described as at least moderate in severity by echocardiography prior to the current admission. Subjects were identified at the time of their admission for decompensated heart failure, i.e., worsening and uncontrolled peripheral oedema or pulmonary oedema defined clinically and on chest radiograph, and approached towards the end of their hospital stay once they were deemed fit to provide informed consent. They were treated for decompensated heart failure with standard medical therapy and discharged from hospital once stable. Potentially suitable subjects were invited to attend for a baseline screening visit between 2 and 4 weeks after their discharge from hospital. Patient information leaflets were provided prior to discharge and again at attendance for baseline assessment. Those patients who were eligible to continue gave consent at this point and proceeded to carry out baseline performance assessments prior to randomisation. Patients were excluded from the study if they were aged <18 or >80 years, had a history of stroke or acute coronary syndrome within the last 3 months, had uncontrolled anginal symptoms or had any respiratory, neurological

or orthopaedic condition which would prevent their participation in either a conventional bicycle exercise training programme or the physical exercise assessments during the study. No subject was participating in any exercise training programme prior to recruitment. At the time of first baseline assessment, participating patients were on standard medical therapy that included ACEi or ARB, diuretic, aldosterone antagonists, digoxin and/or beta-blockers.

3.2 Ethics and consent

Written informed consent was obtained from all subjects participating in studies 1-5. Subjects signed three copies of a standard consent form after confirming that they had read and understood the relevant patient information sheet for the particular study. Consent was taken by myself and witnessed by a research nurse in all cases. The study protocols were approved by the local research ethics committee and conformed to the principles outlined in the Declaration of Helsinki.

3.3 Performance / disease severity assessments

3.3.1 Echocardiography

Echocardiography was performed for studies 1-3 to determine left ventricular ejection fraction (EF). Several techniques are available to quantify LV ejection fraction and include simple visual assessment, M-mode echo, modified 2D Simpson bi-plane method, X-ray cineangiography, radionuclide scanning and cardiac MRI. The most commonly used assessment in clinical practice is a simple visual assessment on 2D echo which is reproducible when performed by experienced sonographers. Visual assessments may

underestimate the severity of LV dysfunction however, and this method along with M-mode and 2D echo assessments of ejection fraction rely on the presence of satisfactory imaging windows and good endocardial border definition (Bellenger *et al.*, 2000). Cardiac MRI may provide the most reproducible assessment of ejection fraction and avoids the limitations of echocardiography with respect to image acquisition. It is not uncommon, however, for patients to be unable to complete an MRI scan due to claustrophobia. Additionally, cardiac MRI is more time consuming and costly at present compared with echocardiography and is not universally available. Cardiac MRI was not available locally at the time the studies were carried out and as such was not considered. Equally, cineangiography and radionucleotide scanning were considered inappropriate as part of our trial design in view of the necessity for radiation exposure.

Accepting the problems associated with image acquisition in 2D echo, studies 1-3 utilised the modified Simpson bi-plane technique to assess LV ejection fraction (Schiller *et al.*, 1989). This technique has been validated previously against radionucleotide scanning and cineangiography (Folland *et al.*, 1979). Each subject underwent two separate scans performed on the same day by a single, experienced sonographer. The mean EF value was used. Where endocardial border definition or apical echo windows were not satisfactory, no assessment was made and the data treated as missing at the time of statistical analysis. Commercial echo contrast agents were not available locally at the time of the studies.

Every subject included in study 4 and every screened subject in study 5 underwent echocardiography as part of their routine clinical care. A prior diagnosis of heart failure

had been made on the basis of symptoms of breathlessness and exercise intolerance accompanied by an echocardiogram reported as showing LV systolic impairment of at least moderate severity. Although ejection fraction is correlated with outcome in heart failure, the relationship between ejection fraction and exercise performance is very poor and as such it was not felt at the time of trial design that a formal ejection fraction was required for these studies as little additional information was likely to be gained. Furthermore, a change in ejection fraction was unlikely to be observed following training owing to the short period of training involved and the reproducibility of measurements between scans – a much larger group of patients would need to be enrolled in these studies to allow meaningful statistical interpretation of any data generated from echo. As such, visual assessment of LV function was considered a valid assessment to confirm that LV systolic dysfunction of at least moderate severity was present.

3.3.2 6-minute walk

The 6-minute walk (6MW) test is a simple measure of how far a subject can walk in 6 minutes. It is well tolerated and theoretically easy to administer (Solway *et al.*, 2001). It is a measure of submaximal exercise performance with patients allowed to rest during the period of the test if they wish. This mirrors daily activities and provides an assessment of the global response to exercise, including cardiac, pulmonary, circulatory, muscular and psychological aspects of exercise. The 6MW test has been used as an outcome measure in chronic respiratory disease (Mackay *et al.*, 2007; Paggiaro *et al.*, 1998; Spence *et al.*, 1993) and heart failure trials of drugs (Barabino *et al.*, 1991;

Hutcheon *et al.*, 2002), devices (Abraham *et al.*, 2002; Higgins *et al.*, 2003) and exercise (Freimark *et al.*, 2007; McKelvie *et al.*, 2002). It is predictive of mortality in CHF (Bittner *et al.*, 1993). Although widely used as an outcome measure, however, improvements in 6MW distance are not always seen, particularly in trials of pharmacological agents which may have included patients with milder symptoms at baseline with less relative improvement in exercise performance after intervention, or the agents themselves having little effect on exercise performance (Olsson *et al.*, 2005). Furthermore, there is evidence that repetition of this test improves the participant's performance making interpretation of test results before and after intervention unreliable (Demers *et al.*, 2001; O'Keeffe *et al.*, 1998; Opasich *et al.*, 1998; Yusuf and Tsuyuki, 1996). Few clinical trials state whether a familiarisation test is performed.

Safety aspects of the 6MW test and contraindications are discussed in the American Thoracic Society guideline (American Thoracic Society, 2002). Patients should ideally use an unobstructed corridor which is 30 metres long with the turn marked with a cone, resulting in a 60 metre circuit. It has been shown that oval circuits may result in longer distances achieved in patients with severe COPD (Sciurba *et al.*, 2003).

No quiet length of corridor was available at the time of the studies and, as such, a 60m square circuit was used. Although this may have resulted in longer distances achieved, the circuit was not altered over the entire study period. The surface was smooth and firm. Seating was arranged at regular intervals to allow the subject to rest, if required. Subjects were rested for at least 10 minutes before the start of the test to allow acclimatisation and to check resting heart rate, blood pressure and to exclude signs of

pulmonary oedema. Subjects wore loose clothing and comfortable shoes. The test was conducted at approximately the same time of the day on each occasion (around 9-10am).

Standardised instructions were given to each subject at the start of the test as follows:

“The object of this test is to walk as far as possible for 6 minutes. You will walk around this hallway continuously turning to your left at each corner. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are allowed to slow down, to stop, and to rest as necessary. You may lean against the wall or sit down while resting, but please resume walking as soon as you are able. I am going to count the number of laps you complete. Remember that the object is to walk as far as possible for 6 minutes, but do not run or jog. If you experience any chest discomfort or dizziness during the test, please stop. Start now, or whenever you are ready.”

To maintain line-of-sight with the subject, one operator stood at one corner of the circuit with the other operator at the opposite corner. The subject was not followed around the circuit and was not encouraged in any way during the test. The subject was informed of the time after 2 minutes, after 4 minutes and 15 seconds before the end of the test.

In view of the training effect seen with two repeated 6MW tests, the test was repeated at least 24 hours later but within 1 week. No strong data exist regarding the effect of performing further practice 6MW tests. Figure 3.1 shows Bland-Altman plots of 6 minute walk distance vs. absolute and percentage difference for 94 consecutive pairs of 6MW tests for CHF patients participating in clinical studies in our department and

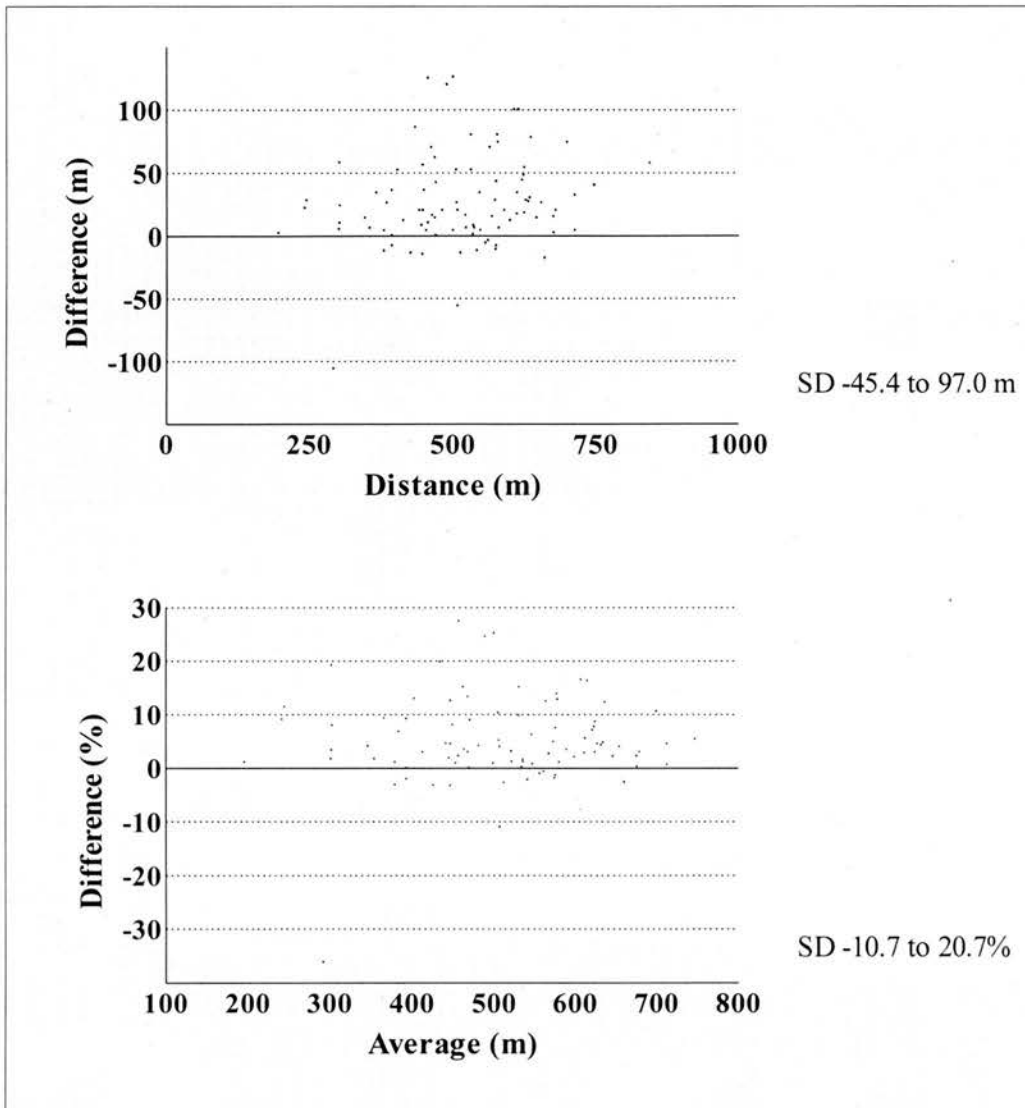


Figure 3.1. Bland-Altman plots for paired 6-minute walk distances. Top: absolute difference; bottom: percentage difference.

performed according to the protocol described above. There is a bias of 25.8 ± 36.3 m or 5.00 ± 8.00 % increase for the second baseline test, respectively.¹ For our study, the first baseline test data was discarded and the second baseline data used as true baseline.

¹ Data presented according to the methods described by Bland and Altman (1999).

3.3.3 Quadriceps strength and fatigue

The exercise training studies employ conventional training using either cycle ergometers or neuromuscular stimulation of the quadriceps and gastrocnemius muscle. To assess change in muscle strength and fatigability after a training period, an immobile quadriceps bench was designed and constructed by the medical physics department at the Western General Hospital, Edinburgh. This employed a piezoelectric strain gauge attached to the bench and was calibrated to provide a measurement of equivalent weight lifted during knee extension. Only the subject's dominant leg was studied (taken as the same side as the hand they would use to write with). Care was taken to position the subject comfortably in the apparatus with their back positioned to ensure a consistent angle of the leg at the knee over the apex of the bench. The shin was placed behind a second pad which was attached to the piezoelectric gauge. The gauge was calibrated by the medical physics department every two months using standard masses. Data from the gauge were analysed on a PC running Microsoft Windows 95™. A program was written specifically for this task and a sample screen print of a demonstration trace is shown in Figure 3.2. This sample simulates a fatiguing test of six-minute's duration. In fact, for the studies presented here, a fatiguing protocol of 20-minutes duration was used, as described by Buller, *et al.* (1991). Firstly, maximum strength was determined as the peak equivalent weight lifted from three maximal voluntary contractions of the quadriceps of the dominant leg and only contractions deemed to be maximal on the basis of the quality of the visual trace were accepted. True maximal contractions demonstrated noise in the visual trace representing fasciculation whereas sub-maximal contractions produced

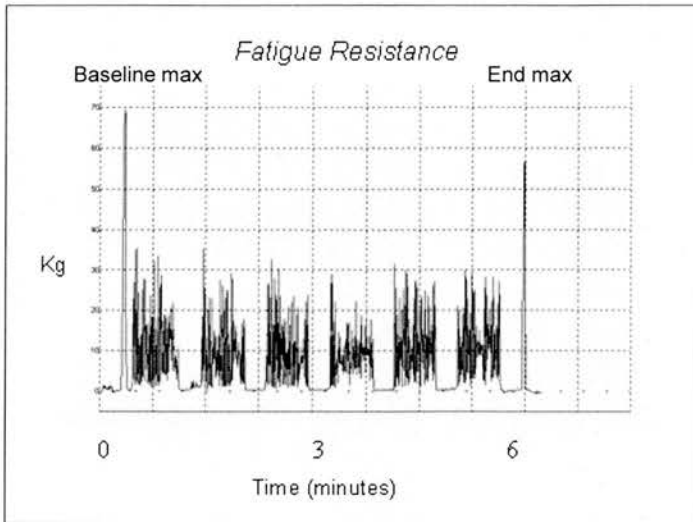


Figure 3.2. Screen print of fatigue protocol measurements.

smooth traces. Attempts were performed at least one minute apart and clear instructions were given to each subject prior to each test. A fatiguing protocol was then performed whereby patients applied a force to the isometric bench at 30% of the previously determined maximum every 2 seconds for 40 seconds of every minute over a 20-minute period. Maximum quadriceps strength was repeated at the end of the 20 minutes and fatigability index expressed as the ratio between the first and second maximal measurements.

Ideally, an instrument such as the Cybex dynamometer would have been used to measure isokinetic strength as this would have removed the potential error introduced by differing leg positions between subjects. Unfortunately, this equipment was not available locally at the time the studies were carried out.

To exclude a training effect similar to that seen with 6MW tests, two baseline tests were performed at least 24 hours apart and the data from the first test discarded. No data exist

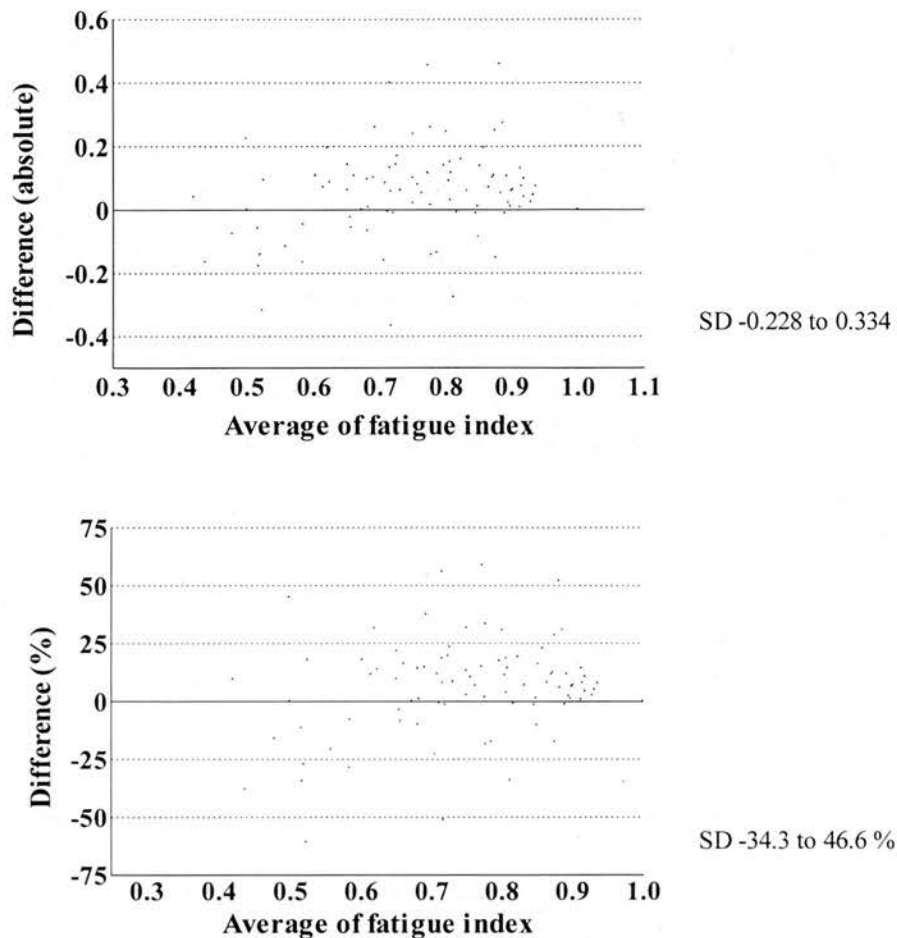


Figure 3.3. Bland-Altman plots for paired fatigue index tests. Top: absolute difference; bottom: percentage difference.

in the literature regarding possible training effects for this type of equipment. Bland-Altman plots of consecutive pairs of strength and fatiguing tests performed on CHF patients according to the protocol described above are shown in Figure 3.3 and Figure 3.4. There was a bias of 2.72 ± 6.21 kg or 6.36 ± 15.1 % for the second test of maximal quadriceps strength and a bias of 0.053 ± 0.144 or 6.15 ± 20.6 % for the second test of fatigue index. Tests were performed at approximately the same time of the day (usually around 10am) and after at least 30 minutes of rest.

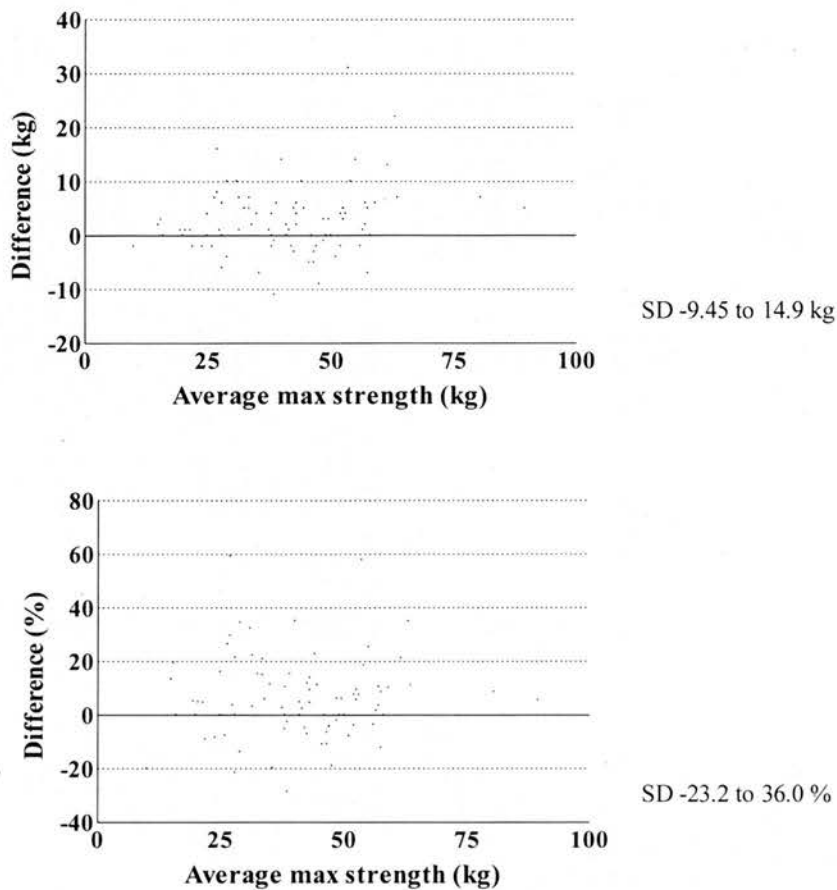


Figure 3.4. Bland-Altman plots for paired maximal quadriceps strength tests. Top: absolute difference; bottom: percentage difference.

3.3.4 Cardiopulmonary data

3.3.4.1 Equipment

Maximum oxygen consumption ($\text{VO}_2 \text{ max}$) is regarded as the best objective assessment of exercise capacity, integrating cardiac, respiratory, circulatory, skeletal, biochemical and psychological performance. Patients rarely achieve a true maximum plateau VO_2 with oxygen consumption limited by one or more variables, e.g., stroke volume, heart

rate or cellular respiration, and so the peak VO_2 attained during exercise is often used as an interchangeable term although it should be appreciated that it is not a true maximal value. Peak VO_2 predicts survival in patients with CHF (Cohn *et al.*, 1993; Francis *et al.*, 1982; Mancini *et al.*, 1991). Oxygen uptake at the lungs directly mirrors tissue oxygen consumption, as shown diagrammatically in Figure 3.5, with CO_2 production at the lungs mirroring cellular CO_2 production under steady state conditions. VO_2 can thus be calculated if one can measure flow and the difference between oxygen inspired and expired as shown in Equation 3.1, where VO_2 is oxygen consumption, VI is the volume of inspired gas (air), FIO_2 is the proportion of oxygen in the inspired gas, VE is the volume of expired gas and FEO_2 is the proportion of oxygen in the expired gas:

$$\text{VO}_2 = [(\text{VI} \times \text{FIO}_2) - (\text{VE} \times \text{FEO}_2)] / t$$

Equation 3.1. Calculation of VO_2

VO_2 is usually expressed per unit time (t) e.g., l/min or ml/kg/min. CO_2 is calculated similarly (Equation 3.2) but with the simplification of removing the minimal quantity of inspired CO_2 from the equation, where VCO_2 is carbon dioxide production, VE is the volume of expired gas, FECO_2 is the proportion of CO_2 in the expirate and t is time:

$$\text{VCO}_2 = (\text{VE} \times \text{FECO}_2) / t$$

Equation 3.2. Calculation of VCO_2

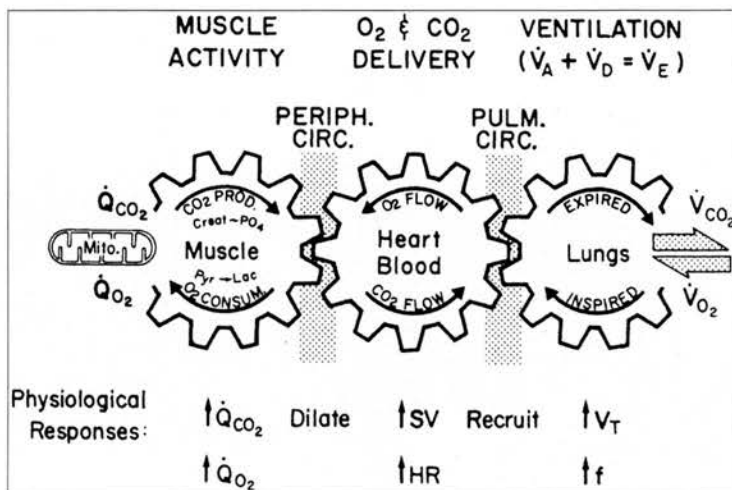


Figure 3.5. Relationship between oxygen consumption and tissue utilisation. Adapted from Wasserman, et al. (2004)

Accurate measurement of oxygen consumption and CO_2 production at the mouth is achieved using specialised cardiopulmonary exercise testing equipment. For studies 1-3, a zirconia fuel cell oxygen analyser and infrared carbon dioxide analyser were used (Benchmark system, Morgan Medical, Kent, UK). For studies 4 and 5 a mass spectrometer system was used (Pulmolab Ex671, Morgan Medical, Kent, UK). Both systems have been demonstrated to provide accurate measurements in the past and are in routine clinical use. The change in equipment between studies 3 and 4 was due to relocation of the studies to the Wellcome Trust Clinical Research Facility (WTCRF) at the Western General Hospital. The previous Benchmark system was owned by the NHS and was in routine clinical use. Due to the large number of patients anticipated to enrol in study 4, it was elected to relocate to the WTCRF and purchase new equipment dedicated to research studies. Cross-validation between the two systems was not performed; however no data collected from either system was shared / pooled with data

from the other as part of any study.

Flow was measured using a pneumotachograph with the Benchmark system (pressure measurement across a low-resistance screen) and a turbine volume transducer with the Pulmolab system (low inertia impeller blades which rotate in response to flow, rotational speed measured by disruption of light beam within volume transducer by impeller blades). Both systems are in routine use around the world and both have potential advantages / disadvantages over the other. Pneumotachographs are cheaper but require laminar flow to function properly and there is greater dead space involved downstream which may affect gas analysis. Additionally, expired gas needs to be as dry as possible as fluid (i.e., saliva) on the low-resistance screen can introduce flow errors. Gas temperature affects this type of flow measuring device more than flow volume transducers. The flow volume transducer is more expensive and less tolerant of damage. Sterilisation is more difficult as hot water melts the impeller blades. There is a potential for lag in flow measurement with this type of system due to the mass of the impeller blades, but this was not encountered as a problem with the Pulmolab system. With both systems, flow was calibrated with a standard 3 litre syringe of air prior to each test. Error tolerance was less than 0.5% for flow calibration.

Prior to exercise, both the Benchmark and Pulmolab systems were calibrated against known gases certified by the manufacturer as accurate in composition to <1%. Expirate was drawn into the tip of the sample capillary tube which was inserted into the mouthpiece at approximately 30ml per minute. This expirate was drawn approximately 2.5 metres along the capillary tube and into either the Benchmark or Pulmolab systems

within a few hundred milliseconds by the vacuum generated by the instrument. A small portion of the expirate was drawn into the vacuum chamber and analysed using a zirconia fuel cell system for O₂ and infrared CO₂ analyser (Benchmark) or mass spectrometer (Pulmolab). With the Pulmolab mass spectrometer system, the expirate is subjected to electron bombardment ionisation and the subsequent ions formed are projected across the quadrupole, under the influence of an electric charge which is dynamically altered to select ions of similar masses. The selected ions carry a current which is collected and measured and is proportional to the ionisation efficiency and partial pressure of the parent molecule, in turn proportional to the concentration of the associated gas. A sample screen print of a mass spectrometer recording for air is shown in Figure 3.6.

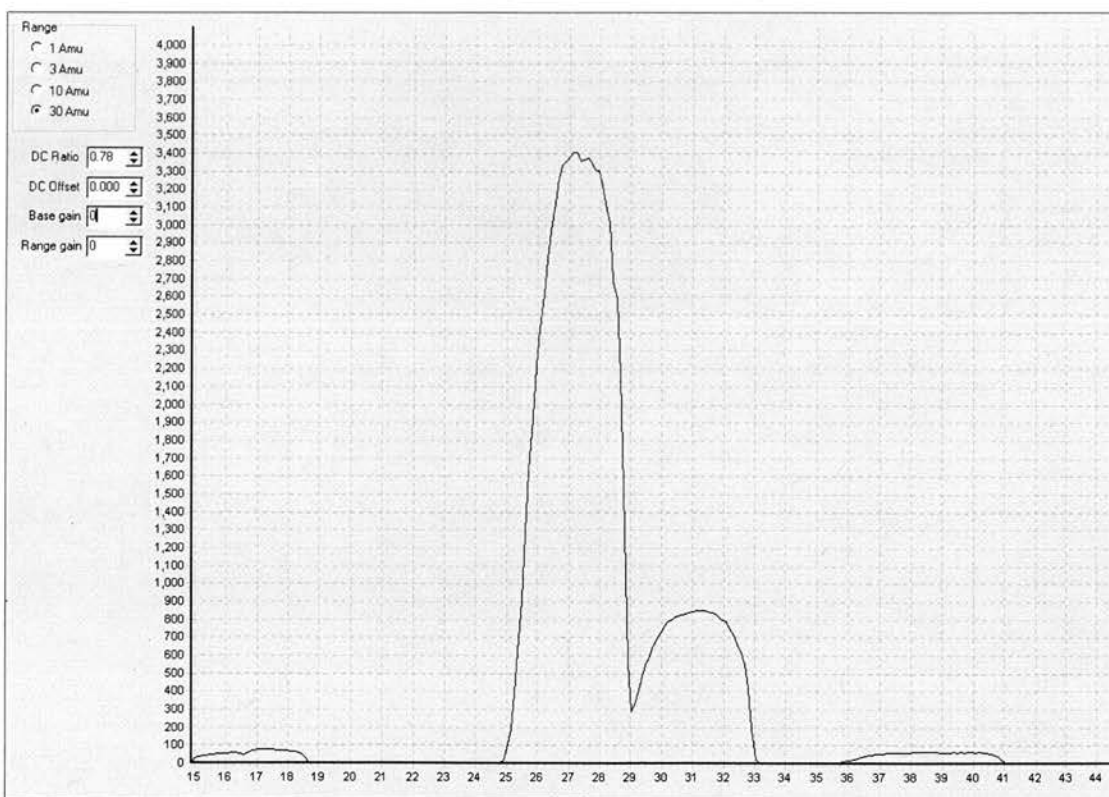


Figure 3.6. Sample mass spectrometer output for room air, Pulmolab ex671.

For both systems, patients exercised on a treadmill using a modified Bruce protocol which consisted of a standard Bruce protocol with the addition of 2 stages occurring before stage 1 of the standard Bruce test: stage 0 at 2.7km/h, 0% slope and stage ½ at 2.7km/hr and 5% slope. Heart rate was recorded continuously. Blood pressure was recorded every 3 minutes, one minute prior to an increase in workload. Patients were encouraged to exercise to the point of exhaustion and this was checked by ensuring that they had achieved their anaerobic threshold (AT), i.e., the point at which metabolic respiration becomes predominantly anaerobic. Assessment of AT is discussed more in section 3.3.4.3.

During exercise, patients were monitored for arrhythmia and were asked to report any symptoms of chest pain or dizziness. The only adverse event noted during over 250 cardiopulmonary exercise tests performed was one episode of non-sustained ventricular tachycardia in a patient with ischaemic cardiomyopathy. The episode lasted less than 30 seconds and the test was terminated on this basis. This occurred at the final assessment visit for a patient participating in study 4 and did not result in exclusion from the study.

Some technical problems were encountered with the purchase and installation of the Pulmolab system which had a direct impact on study 4. There was a six-month delay between ordering of the equipment and final installation and full integration with treadmill, cycle ergometer exercise equipment and 12-lead ECG analysis equipment. This in turn led to a delay in patient recruitment into study 4. Additionally, calibration issues were identified relating primarily to the quadrupole mass spectrometer. Impurities on the surface of the quadrupole resulted in inaccurate measurements of oxygen and

carbon dioxide. Cardiopulmonary testing was therefore unavailable for several weeks during the course of study 4 further limiting patient recruitment. Finally, combination of ECG and cardiopulmonary real-time data analysis on a single PC proved problematic. The PC was considered state-of-the-art in 2002 but did not have sufficient multi-tasking processing power to cope with the heavy demands placed upon it. Integration of flow and gas data analysis is critical for generation of accurate cardiopulmonary data and there were concerns at the beginning of study 4 regarding the validity of some results obtained. These results were discarded and following discussion with the manufacturer, a replacement PC was provided. Once these issues were resolved, the equipment proved reliable and, with careful calibration, accurate. The accuracy and validity of cardiopulmonary data presented in all of the below studies was not thought to have been adversely affected by the commissioning issues.

3.3.4.2 Peak VO_2

Analysis of breath by breath data obtained by both systems was performed off line. Raw data was not available from the Benchmark system; data was averaged over 8 retrospective rolling breaths. Peak VO_2 was taken as the maximal VO_2 in the last 30 seconds of exercise. A similar system was employed for data obtained from the Pulmolab system. Raw data was used and retrospectively analysed using the Morgan Medical analysis suite software (MMAS). A rolling average of 8 breaths was used and peak VO_2 taken as the highest VO_2 in the final 30 seconds of exercise.

3.3.4.3 Anaerobic threshold

Anaerobic threshold (AT) is a submaximal exercise parameter which has been shown to be associated with prognosis (Gitt *et al.*, 2002) and which can increase following a period of exercise training as discussed in section 2.3.2.4 (Hambrecht *et al.*, 1995; Wielenga *et al.*, 1999). It is usually expressed as an absolute value referenced to the VO_2 at which the threshold occurs, and as a percentage of predicted peak VO_2 . It is usually around 50-60% of predicted VO_2 . It is the point at which cellular respiration becomes predominantly anaerobic. During incremental exercise, a combination of oxygen delivery and consumption mismatch plus probable recruitment of muscle fibres with a predominantly glycolytic metabolism contribute to the generation of lactic acidosis. The term lactate threshold is sometimes used when describing this phenomenon but should be reserved for studies where lactic acid has been sampled invasively. Buffering of lactate occurs with stimulation of respiration and increased CO_2 exchange at the lungs. This along with the contribution of anaerobic cellular metabolism leads to higher VCO_2 compared to VO_2 . The point at which this occurs is the AT and it can be determined by different techniques. The most commonly used technique is the modified V-slope method (Sue *et al.*, 1988) which simplifies the original complex V-slope method (Beaver *et al.*, 1986). VCO_2 increases as a linear function of VO_2 in early exercise below the anaerobic threshold (S1). As exercise intensity increases with increased lactate production, there is an increase in slope (S2). Plotting VO_2 against VCO_2 allows the visual determination of AT, termed the break point (Figure 3.7).

Problems exist with this assessment of AT, however. Acute hyperventilation will

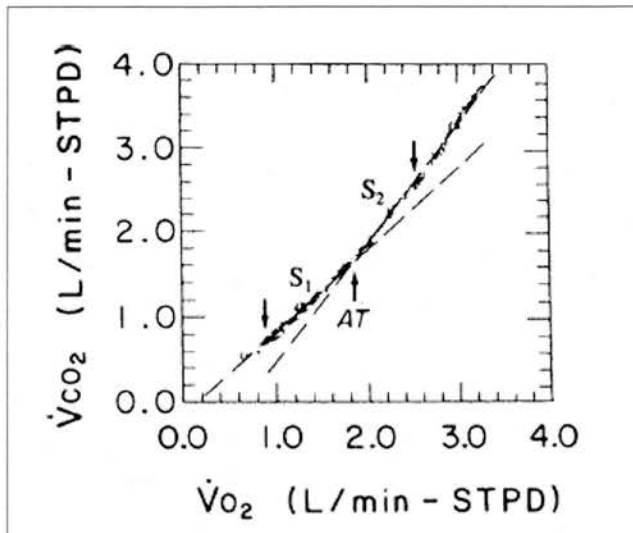


Figure 3.7. Measurement of anaerobic threshold by V-slope method. Adapted from Beaver et al., 1986.

increase $\dot{V}CO_2$ disproportionately to $\dot{V}O_2$ in the absence of significant lactate buffering. Abnormal breathing patterns will also invalidate the V-slope method of non-invasive determination of anaerobic threshold. Additionally, computerised graphical displays of $\dot{V}O_2$ vs. $\dot{V}CO_2$ allow manual positioning of trend lines across the data representing S1 and S2. The data is usually averaged which invalidates the concepts of linear regression on which the automated trend lines are based. Secondly, the manual positioning is arbitrary and frequently varies between operators and even with the same operator and test when analysed on separate occasions. To counteract these problems, two solutions were employed. Firstly, I designed an automated system allowing two linear regression lines to be 'best-fit' plotted against raw data. Graphpad Prism 4.0 was programmed with the following instruction set (Equation 3.3):

$$\begin{aligned}
 Y1 &= \text{intercept} + \text{slope1} * X \\
 Y_{atX0} &= \text{slope1} * X0 + \text{intercept1} \\
 Y2 &= Y_{atX0} + \text{slope2}(X - X0) \\
 Y &= \text{IF}(X < X0, Y1, Y2)
 \end{aligned}$$

Equation 3.3. Automated break-point calculation using 'bi-linear' regression to determine anaerobic threshold.

This allowed linear regression equations to 'best-fit' above and below a break point in the raw data which would otherwise have been difficult to determine visually. An example of data produced is shown in Figure 3.8. Secondly, values obtained by this V-slope method were checked using the ventilatory equivalents method. VE/VO_2 and

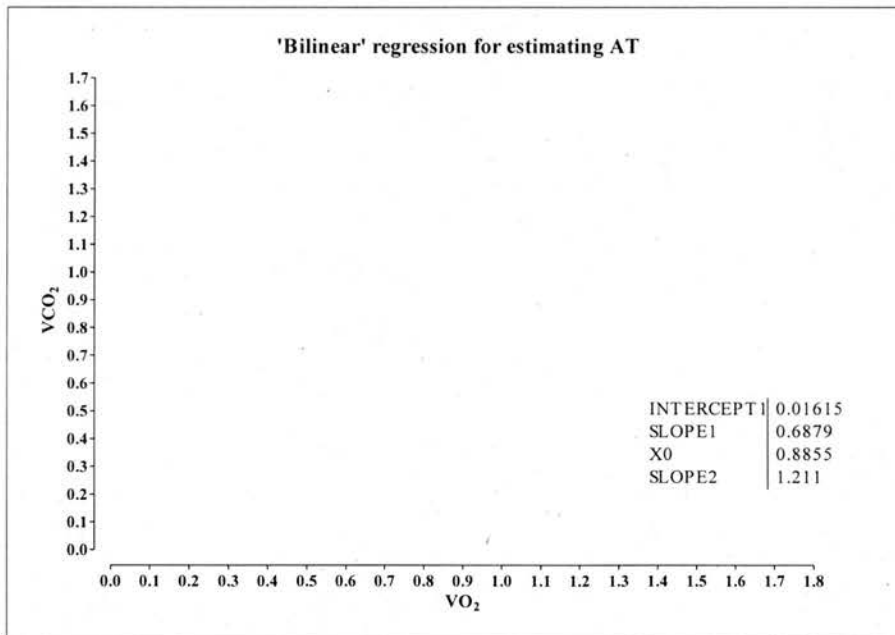


Figure 3.8. Example of 'bi-linear' regression fitting to calculate anaerobic threshold from raw cardiopulmonary data.

VE/VCO₂ were plotted and AT assessed as the VO₂ where VE/VO₂ reaches a minimum and begins to rise without a rise in VE/VCO₂.

No data yet exist regarding the correlation between AT determined by the regression technique described above and invasive measurement of lactate threshold, but this could be included in future research.

3.3.4.4 VE/VCO₂ slope

VE/VCO₂ slope is a measure of ventilatory efficiency. It represents the amount of ventilation required to eliminate CO₂ produced during respiration. As discussed in section 2.3.2.4, there is an exaggerated ventilatory response to exercise in CHF (Beaver *et al.*, 1986; Gitt *et al.*, 2002) which is independently predictive of mortality (Arena *et al.*, 2003; Corra *et al.*, 2002) and with beneficial change seen following exercise training (Coats *et al.*, 1992; Guazzi *et al.*, 2004). At low levels of exertion and at rest, the relationship between VE and VCO₂ can be random, being influenced by situational and psychological factors. At heavy exertion, the relationship is non-linear, being influenced by the degree of lactate production and CO₂ production / buffering. At moderate levels of exercise, however, the relationship is linear and most investigators use the linear portion of the slope prior to the AT to generate the data. This was the method used in these studies. There is some data, however, to suggest that VE/VCO₂ slope remains a strong predictor of morbidity and mortality irrespective of the portion of the exercise test data used (Arena *et al.*, 2003). Raw data was analysed off-line using Microsoft Excel version 2000™ after determination of the AT. Data after the onset of AT, resting pre-test

data and data from the first 1-2 minutes of exercise which was clearly non-linear were excluded.

3.3.4.5 Oxygen Uptake Efficiency Slope

The oxygen uptake efficiency slope (OUES) was originally proposed as a submaximal measure of performance without the need for maximal effort tolerance (Baba *et al.*, 1996). It is the linear portion of the relationship between VO_2 and the logarithmic plot of VE and is defined by Equation 3.4, where a is the OUES and b is the intercept on the y axis:

$$\text{VO}_2 = \text{a} \cdot \log_{10} \text{VE} + \text{b}$$

Equation 3.4. Oxygen uptake efficiency slope (OUES).

It has been shown to be a predictor of mortality in univariate and multivariate analysis models in a retrospective analysis, and values are significantly lower with worsening NYHA functional class (Davies *et al.*, 2006). Little data exist regarding the effects of exercise training on OUES although a recent small study suggested an early beneficial change (Van *et al.*, 2007). There is no consensus regarding the use of data from the entire test or truncated data, e.g. before the onset of AT, but it has been suggested that values derived from truncated data vary little from those values derived from an entire test (Davies *et al.*, 2006). Raw data was not readily available for OUES determination for studies 1 to 3. As such OUES was included as an analysis variable in studies 4 and 5 only. Raw data from the linear portion of the test prior to onset of AT and excluding pre-test resting data and the first 60 seconds of exercise was used. Data was analysed using Microsoft Excel version 2000™.

3.3.5 DEXA scanning

Studies 1-3 use data derived from dual-energy x-ray absorptiometry. Patients underwent DEXA scanning prior to randomisation and at the end of the studies. The mean time from end of the exercise training period to the final scan was 1.53 ± 1.39 months, range 1 day to 5.32 months). The scanner was in routine NHS use and delay in performing the second scan was due to limited scanner time availability. The Hologic QDR 4500A DEXA scanner was used (Hologic, USA) which employs a whole-body dual energy fan-beam scanning technique. Measurement of lean tissue mass and fat mass by this technique has been validated previously (Salamone *et al.*, 2000; Visser *et al.*, 1999). Two scans were performed on each occasion and analysed using *Hologic Software* version 11.1. A mean of the two measurements was used to improve accuracy. Whole body densitometry scanning was used to calculate fat free mass, skeletal muscle mass and total body bone mineral density. Bone density is expressed as g/cm^2 and as a standardised t-score, which compares individual bone density values with those of a young sex-matched population and a standardised z-score, which compares individual values with those of an age and sex-matched population. According to World Health Organisation criteria, t-scores less than -2.5 (indicating bone mineral densities more than 2.5 standard deviations below the mean) represent osteoporosis, and t-scores between -1 and -2.5 represent osteopenia.

Total radiation exposure for each pair of scans was approximately $7\mu\text{Sv}$, which is equivalent to one day of normal background radiation in the UK.

3.3.6 Cytokine analysis

For study 3, cytokine and high sensitivity C reactive protein (hs-CRP) analyses were performed. Samples were drawn at the first baseline visit and at the time of post-training assessment. Subjects rested in an armchair for at least 30 minutes in a quiet environment before samples were drawn by an investigator experienced in phlebotomy. A tourniquet was used. Samples were drawn prior to any exercise assessment and at approximately the same time of day, i.e., usually at around 8:45am after completion of enrolment paperwork. Venous blood was drawn into vacuum serum gel containers which were then stored on ice prior to being centrifuged within 1 hour at 1000G and 4°C for 10 minutes. Supernatant was stored at -80°C. Serum levels of TNF α , sTNF $_{r1}$, sTNF $_{r2}$ and IL-6 were measured locally using commercially available enzyme immunoassay kits according to the manufacturer's recommendation (Quantikine, R&D Systems, USA). Precision and sensitivity for the assays are as follows: IL-6 intra-assay precision 4.2%, inter-assay precision 6.4%, sensitivity 0.7pg/ml; TNF α intra-assay precision 4.6%, inter-assay precision 5.4%, sensitivity 4.4pg/ml; sTNF $_{r1}$ intra-assay precision 6.9%, inter-assay precision 8.8%, sensitivity 3pg/ml; sTNF $_{r2}$ intra-assay precision 2.5%, inter-assay precision 5.1%, sensitivity 1pg/ml. Hs-CRP was not analysed locally. This analysis was performed by the Department of Biochemistry, Royal Victoria Hospital, Kirkcaldy, Fife. Samples were held locally until the time of analysis and transported within one hour insulated and on dry ice. The enhanced immunonephelometry technique was used for analysis (Dade Behring, Marburg, Germany) (Montagne *et al.*, 1992). Sample data remained blinded until the time of final data analysis.

3.3.7 NT-pro BNP analysis

Blood sampling for studies 4 and 5 was performed in a similar fashion to the cytokine sampling described in section 3.3.6 above. Samples were drawn at the first baseline visit and at the post-training period visit approximately six weeks later. Sampling was performed after at least 30 minutes of rest in a quiet undisturbed room. Patients relaxed in an arm chair during this period. The same time of the day was typically used, prior to any exercise assessments (usually around 8:45am). A tourniquet was used. Samples were collected into a non-vacuumed syringe and immediately spun using a centrifuge in the adjacent room at 4 degrees centigrade for 20 minutes at 1000G. Supernatant was collected and immediately stored at -80°C. Samples were sent in one batch at the end of the study period to the Department of Biochemistry, Glasgow Royal Infirmary insulated and on dry ice. N-terminal pro BNP (NT pro-BNP) analysis was performed using a standard assay (Roche Diagnostics, Basel, Switzerland). Sample data remained blinded until the time of final data analysis.

3.3.8 Quality of life

Patients participating in studies 1-3 completed a Minnesota 'living with heart failure' questionnaire at the first baseline visit between exercise performance assessments and at the end of the training period. A copy of this questionnaire and instructions for data collection and storage are provided in Appendix A. This questionnaire has been widely used for over 15 years as an outcome measure in heart failure and has been designed to be representative of the ways in which CHF affects quality of life, including, physical,

emotional, social and psychological aspects. In addition to questions regarding physical functioning, such as the impact of breathlessness, fatigue, etc., other questions explore issues such as ability to earn a living, social impact on carers, memory and concentration and side effects of therapy. It has been demonstrated to be reliable and reproducible (Bennett *et al.*, 2003; Gorkin *et al.*, 1993; Rector and Cohn, 1992). A number of clinical trials have demonstrated changes in the treatment arm of the study but no change in the placebo arm, indicating the responsiveness of the questionnaire to change, e.g., trials of ACEi / ARB (Cohn and Tognoni, 2001; Rector *et al.*, 1993), heart failure disease management programmes (Harrison *et al.*, 2002; Kasper *et al.*, 2002), resynchronisation therapy (Abraham *et al.*, 2002; Young *et al.*, 2003) and exercise training (Belardinelli *et al.*, 1999). The use of this questionnaire over a short period of exercise training has not been tried before, however.

3.4 Exercise training

3.4.1 Randomisation

Patients enrolled in studies 1-3 were randomised after completing the second baseline assessment. This was to ensure that they were able to complete the functional performance assessments required in the study prior to randomisation. Randomisation was performed according to a pre-defined schedule by a third party with the investigator and subject having no prior knowledge of the schedule.

Patients enrolled in study 4 were randomised in a similar fashion with a predetermined block schedule designed and administered by an independent statistician in the WTCRF.

Again, patients were only randomised once the second baseline assessment visit was complete, and no prior knowledge of the schedule was available for the subject, investigator or research nurse. The block randomisation schedule was based on equal randomisation between the three groups (control, bike and neuromuscular stimulation, NMS) over the anticipated recruitment of 120 subjects.

3.4.2 Cycle ergometer training

The bicycle exercise regimes for studies 1-3 and studies 4 and 5 were similar, although different equipment was used. Patients participating in studies 1-3 and assigned to the bicycle group underwent a 1-hour instruction session in the use of a semi-recumbent bicycle and a chest-strap/wrist heart rate monitor (Polar, UK). The bike was adjusted to provide the maximum comfort for the subject. A peak heart rate was determined as the mean of the peak heart rates from the two preceding maximal treadmill exercise tests. Subjects were asked to exercise on the bike sufficiently to achieve 70% of this maximum heart rate. To achieve this, they were asked to adjust the resistance of the bike manually and alter their speed as necessary. Subjects were issued with a diary card to record the duration and peak heart rate achieved whilst exercising. They were asked to exercise for 30 minutes per day, five days per week for 6 weeks. The first 3 sessions were of shorter duration to allow acclimatisation. Bicycles were delivered to the subjects' homes and placed in a convenient position. The bikes were collected at the end of the study.

Patients participating in studies 4 and 5 and assigned to the bicycle exercise group were

assessed for their maximum heart rate in the same way, i.e., from the previous treadmill tests. Rather than using Polar chest strap / wrist watch heart rate monitors, however, a combined heart rate monitor / ergometer system was used. Patients were given approximately 1 hour of training with a Kettler SX1 recumbent cycle (Kettler, UK). This system monitored heart rate via sensors in the handles and could vary resistance at the wheel electromagnetically. Bikes were programmed to automatically adjust workload to maintain a constant heart rate of between 75 and 85% of the previously determined maximum. Subjects were asked to exercise for 30 minutes per day, five days per week for six weeks. The first 5 training sessions were shorter to allow acclimatisation. Patients kept an exercise diary; additionally, odometer recordings from the equipment could be checked to verify compliance at the end of the training period. Bikes were delivered by a professional delivery company to the subjects' homes and collected at the end of the training period.

No significant technical difficulties were experienced with either cycle type. Patients appeared to prefer the Kettler system used in studies 4 and 5 as adjustment of workload was performed by the bike automatically. The heart rate sensors in the Kettler bike appeared to cope with atrial fibrillation adequately. The only adverse comments received from patients regarding the bikes was that they were large and heavy – once it had been positioned in the subject's house, it was difficult for a patient to move.

3.4.3 Neuromuscular electrical stimulation

The protocol for use of NMS was slightly different between studies 1-3 and studies 4

and 5. For studies 1-3, patients randomised to the NMS group received approximately one hour of hospital-based training in the use of the device, specifically relating to adjustment of electrode position and stimulator output in order to achieve maximal muscle recruitment. Commercially available muscle stimulators and electrodes were used (Sports Pro, Boditek Ltd, UK). Each stimulator has 4 output channels, each supplying a pair of electrodes. This allowed positioning of electrodes on the skin over the upper-lateral and lower-medial aspects of the quadriceps muscle of both legs and over the upper and lower portions of gastrocnemius muscles of both legs. Specifically, the first electrode pair was positioned approximately 5cm below the inguinal fold and approximately 5cm above the upper patella border; the second electrode pair was positioned over the belly of the gastrocnemius muscle approximately 2cm below the popliteal fossa and approximately 2cm above the junction between gastrocnemius and achilles tendon. The stimulator was configured to deliver a direct electrical current at 25 Hertz (Hz) for 5 seconds followed by 5 seconds of rest. The intensity of the stimulation was adjusted by the patient to achieve a visible muscle contraction that was not sufficiently strong to cause discomfort or a significant movement at either the knee or ankle joints. Due to acclimatisation, patients were required and encouraged to gradually increase the stimulator output over 30 minutes of stimulation. At the end of the stimulation period, the adhesive electrodes were stored to prevent drying of the conductive gel and a diary of stimulator settings completed.

Patients participating in studies 4 and 5 used identical stimulator units with the same electrode configuration. They also underwent the same period of training and were

encouraged to maintain a diary. They used the stimulators for 30 minutes per day, 5 sessions per week for 6 weeks. Again, stimulation was applied for 5 seconds every 10 seconds. Signal frequency was adjusted to alternate between 25Hz and 50Hz daily. This was performed as it is possible that stimulation at different frequencies may preferentially recruit different muscle fibre types, possibly with the 50Hz cycle frequency preferentially recruiting fast-twitch fibres. However, no data exist in the literature to confirm this theory.

3.5 CHF population screening

To assess the characteristics of a large population of CHF patients and to enable their follow-up, I designed and programmed a multi-relational database. This was created in *Microsoft Access* version 10 (2000). The core dataset includes demographic data and health-related data including medications and investigations. All patients admitted to the Western General Hospital between October 2001 and December 2003 were screened in hospital and those with a proven diagnosis of heart failure due to left ventricular systolic impairment were entered into the registry. Screening was carried out by reviewing the notes of patients admitted and by scrutinising discharge summaries. The diagnosis of CHF was made on the basis of consistent symptoms and echocardiographic evidence of LV systolic impairment. The patient was interviewed and where necessary examined by either a heart failure specialist nurse or a cardiologist. Diagnosis may have been made on a prior admission. The likely duration of heart failure prior to entry into the database was recorded. Details were updated by the heart failure nurse liaison team when patients reattended for clinic review, at home visits, for beta-blocker up-titration on the day-care

unit, when attending for other research studies, at the time of readmission, and at the time of death. Although the database is used across multiple sites in Lothian and Fife, only data pertaining to patients admitted to the Western General Hospital in Edinburgh was used for study 5. Permission was asked from patients before their data was included in the registry. The database is registered under the data protection act, registration number K4245548. The database relationships are depicted in Appendix B.

Data was extracted from the database with SQL queries designed in *SPSS for Windows* version 13, at which point data were anonymised.

3.6 Statistical analysis

3.6.1 Power calculation

Study 1 was designed as a proof-of-concept pilot. No control group was included. The sample size was estimated on the basis of improvement in peak VO_2 following training. From previous studies involving short programmes of training vs. control populations, an increment of around 15-30% in peak VO_2 has been observed (see Table 2.4). Assuming a peak VO_2 for a sample of NYHA class II and class II patients of around 20 ml/kg/min, if only 10% improvement in peak VO_2 following NMS training was observed, but 20% improvement following bike training, this would result in post-training peak VO_2 measurements of 22 and 24 ml/kg/min, respectively. Hence, there would be a difference between the two groups of around 2 ml/kg/min, potentially. Taking an α of 0.05, a difference between the two group means of 2 ml/kg/min, a power of 0.99 and an arbitrary standard deviation of difference between the two means of 3

ml/kg/min, this results in a sample size of 44 required to reject the null hypothesis that the two groups show no difference in the effect of training on peak VO_2 . If the projected difference between the two groups is proved to be less, the sample size required would be much larger. It is the nature of the pilot study, however, that these differences are unknown at the outset.

Following the results of study 1, a further power calculation was performed to assess the sample size required to show a difference between NMS, bike training and controls. Assuming an increase of just 5% in peak VO_2 following training with either regime, an α of 0.05, a standard deviation within groups of 2 ml/kg/min and a difference between groups of 1 ml/kg/min, the power calculation based on an ANOVA model with 40 patients within each group results in a power of 0.598. Comparing combined data from both exercise regimes with controls using the same parameters as above yields a statistical power of 1.0. The actual difference between groups and standard difference between group means may not be judged correctly, however, leading to an underestimate of sample size.

3.6.2 Analysis

All analysis was performed using commercially-available software running on *Microsoft Windows*TM. Data remained blinded until the final analysis. Advice and assistance was provided by professional statisticians working for the University of Edinburgh (studies 1-3) and the WTCRF (studies 4,5). *SPSS for Windows* version 13.0, *GraphPad Prism* version 4.0 and *Microsoft Excel* version 11 (2003) were used where appropriate.

Individual statistical tests vary between studies and are detailed in the methods section of the relevant data chapters.

4 Study 1. A randomised study of home-based neuromuscular stimulation of the legs and conventional bicycle exercise training for patients with chronic heart failure.

4.1 Abstract

4.1.1 Aims

Recent guidelines recommend regular exercise in the management of patients with chronic heart failure. This study was designed to compare the safety and efficacy of conventional bicycle exercise and functional electrical stimulation of the legs as forms of home-based exercise training for stable chronic heart failure patients and is the pilot study for further work presented in this thesis.

4.1.2 Methods and Results

46 patients (38 male) with stable NYHA Class II/III heart failure underwent a six-week training programme using either a bicycle ergometer or neuromuscular stimulation of the quadriceps and gastrocnemius muscles. In the bike group significant increases were seen in 6-minute walk (44.6m, 95%CI 29.3 to 60.9m), treadmill exercise time (110s, 95%CI 72.2-148.0s), maximum leg strength (5.32kg, 95%CI 3.18-7.45kg), and quadriceps fatigue index (0.08, 95%CI 0.04-0.12) following training. In the stimulator group similar significant increases were seen following training for 6-minute walk (40.6m, 95%CI 28.2 to 53.0m), treadmill exercise time (67s, 95%CI 11.8-121.8s), maximum leg strength (5.35kg, 95%CI 1.53-9.17kg), and quadriceps fatigue index (0.10, 95%CI 0.04-0.17). Peak VO_2 did not change in either group following training, indicating a low-

intensity regime. Quality of life scores were improved following training when the bicycle and stimulator groups were considered together but not separately (-0.43, 95%CI -8.13 to -0.56).

4.1.3 Conclusions

Neuromuscular stimulation produces beneficial changes in muscle performance and exercise capacity in patients with chronic heart failure. Within this study, the benefits were similar to those observed following bicycle training. Neuromuscular stimulation could be offered to heart failure patients as an alternative to bicycle training as part of a home-based rehabilitation programme and further work is required to clarify the benefits of this form of training.

4.2 Introduction

A number of recently published guidelines recommend a regular programme of exercise training for patients with CHF (Hunt *et al.*, 2001; Remme and Swedberg, 2002; Scottish Intercollegiate Guidelines Network, 2002; Working Group on Cardiac Rehabilitation & Exercise Physiology and Working Group on Heart Failure of the European Society of Cardiology, 2001). The majority of previous studies of exercise training in CHF have been hospital based (Belardinelli *et al.*, 1995b; Belardinelli *et al.*, 1995a; Belardinelli *et al.*, 1999; Dubach *et al.*, 1997a; Jette *et al.*, 1991; Wielenga *et al.*, 1999) although there are now a number of studies confirming the effectiveness of home-based programmes (Adamopoulos *et al.*, 1993; Coats *et al.*, 1992; Hambrecht *et al.*, 1995; Hambrecht *et al.*, 2000a). The ability to deliver such programmes within primary and secondary care is limited by available resources and safety concerns. In addition, co-morbidities that limit

the ability to perform exercise are common in CHF patients, particularly the elderly (Lien *et al.*, 2002) and some have such marked impairment of exercise capacity that they may be unable to undertake physical training.

Neuromuscular stimulation (NMS) is a method of exercising which requires less baseline functional capacity to perform. It has been studied in other patient groups who cannot undertake conventional forms of exercise, e.g. patients with scoliosis (Grimby *et al.*, 1985; Wright *et al.*, 1992), muscular dystrophy (Zupan, 1992) and paraplegia (Hjeltnes and Lannem, 1990). It is recognised to improve muscle fatigue resistance and muscle strength depending on the pattern and frequency of the electrical impulses used (Bajd *et al.*, 1989). NMS of the lower limb muscles is potentially attractive as a method of training in chronic heart failure as it is home-based, requires less motivation to use and could be performed by patients unable to undertake conventional training due to their symptoms of heart failure or other co-morbidities. Additionally, the devices are widely available and relatively inexpensive, typically costing around 160-250 Euros. However, NMS has not been extensively investigated in patients with chronic heart failure. Two small trials found NMS to produce improvements in muscle strength and metabolic measures of exercise capacity in highly selected patients around the time of cardiac transplantation (Quittan *et al.*, 2001; Vaquero *et al.*, 1998). One further small uncontrolled trial in less symptomatic patients also demonstrated the safety of NMS and suggested improvements in quality of life and exercise capacity (Maillefert *et al.*, 1998). I have therefore compared the usefulness and tolerability of NMS with conventional bicycle training for a group of stable chronic heart failure patients in a six-week home-

based randomised study.

4.3 Methods

4.3.1 Study Population

Patients with stable heart failure and New York Heart Association class II-III symptoms were recruited from out-patient clinics as described in section 3.1.1. All subjects were limited in their ability to perform exercise by either breathlessness or fatigue as a consequence of heart failure and were on appropriate medical therapy including angiotensin converting enzyme inhibitors (ACEi), diuretic, digoxin and beta-blockers (Table 4.1). None of the subjects was participating in an exercise programme prior to inclusion in the study. Exclusion criteria as discussed in section 3.1.1 applied. Written informed consent was obtained from all subjects and the protocol was approved by the

	Bike group (n=24)	NMS group (n=22)	<i>p</i> value
Age \pm SD, years	61.8 \pm 10.8	63.0 \pm 10.0	0.68
Sex, n (%)			
Male	21 (87.5)	17 (77.3)	0.30
Female	3 (12.5)	5 (22.7)	
CHF aetiology, n (%)			
IHD	16 (66.7)	13 (59.1)	0.60
DCM	8 (33.3)	9 (40.9)	
NYHA Functional class, n (%)			
II	18 (75)	17 (77.3)	0.86
III	6 (25)	5 (22.7)	
Ejection fraction \pm SD, %	32.0 \pm 9.3	28.3 \pm 6.3	0.008
Medications, n (%)			
Diuretic	17 (71)	20 (91)	0.09
ACEi	22 (92)	22 (100)	0.27
Spironolactone	1 (4)	3 (14)	0.27
Digoxin	9 (38)	10 (45)	0.58
Beta-blocker	9 (38)	9 (41)	0.81

Table 4.1. Patient characteristics at baseline.

local research ethics committee.

4.3.2 Patient assessment

At baseline, patients underwent 6-minute walk test (section 3.3.2), cardiopulmonary treadmill exercise test (section 3.3.4) and quadriceps strength and fatigue testing (section 3.3.3) on two separate occasions at least 24 hours apart to familiarise them with assessments prior to randomisation. Results recorded at the second baseline visit were used as the pre-training values in the final analysis. Ejection fraction was measured on echocardiography by the Simpson biplane method at one of the baseline visits (section 3.3.1). The Minnesota 'living with heart failure' quality of life questionnaire was completed at the first baseline visit prior to the exercise performance tests (section 3.3.8). All assessments other than echocardiography were repeated on one occasion after the exercise training period.

4.3.3 Exercise training

Patients were randomised following baseline assessment to receive either a recumbent bicycle ergometer or NMS for home use over a 6-week period as described in section 3.4.1. Those patients assigned to the bicycle group were trained to use the equipment and asked to exercise for 30 minutes per day, 5 days per week for 6 weeks as described in section 3.4.2. Patients allocated to use NMS were also trained in their use and asked to use the devices for 30 minutes per day, 5 days per week for 6 weeks, as described in section 3.4.3. There were no scheduled hospital visits during the training period. Subjects from both groups maintained a diary indicating the duration and intensity of exercise during each session over the training period. This diary was compared against

subjects' verbal description of their experience with either the bike or muscle stimulator.

4.3.4 Statistical analysis

All data are expressed as mean \pm SD unless otherwise stated. Normally distributed paired data was compared using a paired t-test and unpaired data with an unpaired t-test or a Pearson Chi-square test with Fisher's exact test where appropriate. A Mann-Whitney U test was used to compare unpaired data that were not normally distributed. One-way ANOVA was used to compare mean data at different time-points during the study. Analysis was performed using *SPSS for Windows* version 13.0. A value of $p < 0.05$ was considered statistically significant.

4.4 Results

49 patients were recruited and 46 completed the exercise training programme. Of the three who did not complete the study, one patient died following randomisation to the NMS due to increasingly severe heart failure, one patient assigned to NMS dropped out of the study due to worsening symptoms of heart failure and one patient assigned to the bicycle group dropped out of the study due to back discomfort. Baseline data for these patients were included in the final analysis with post-training data treated as missing data. Of the remaining 46 patients, no adverse effects were reported and their medical therapy remained unchanged for the duration of the study. Blood pressure and heart rate was recorded in five patients who underwent a 30-minute period of electrical stimulation of the quadriceps and gastrocnemius muscles and no acute changes were observed during stimulation (data not shown). Baseline characteristics for those patients who completed the exercise training programme are detailed in table 1. Patients in the NMS

	Whole group n=46	Bike group n=24	NMS group n=22
<i>Exercise time (s)</i>			
pre-training	524 ± 37	544 ± 58	501 ± 43
post training	614 ± 40	654 ± 58	568 ± 53
p-value	<0.001	<0.001	0.020
<i>Peak VO₂ (ml/kg/min)</i>			
pre-training	18.8 ± 0.84	19.0 ± 1.14	18.6 ± 1.27
post training	19.3 ± 0.77	19.8 ± 1.10	18.6 ± 1.07
p-value	0.380	0.276	0.932
<i>Quadriceps strength (kg)</i>			
pre-training	45.7 ± 2.0	48.8 ± 3.0	42.3 ± 2.6
post training	51.0 ± 2.2	54.1 ± 3.3	47.6 ± 2.9
p-value	<0.001	<0.001	0.009
<i>Quadriceps fatigue</i>			
pre-training	0.77 ± 0.03	0.76 ± 0.03	0.77 ± 0.03
post training	0.86 ± 0.02	0.84 ± 0.03	0.88 ± 0.02
p-value	<0.001	0.001	0.005
<i>6-minute walk distance (m)</i>			
pre-training	493 ± 18	495 ± 24	491 ± 26
post training	536 ± 17	540 ± 23	531 ± 25
p-value	<0.001	<0.001	<0.001
<i>Quality of life score</i>			
pre-training	32.7 ± 3.16	36.3 ± 4.21	28.7 ± 4.70
post training	28.4 ± 2.91	31.0 ± 3.66	25.5 ± 4.61
p-value	0.024	0.105	0.094

Table 4.2. Training-induced changes in exercise capacity and quality of life.

group had a lower ejection fraction at baseline but otherwise there were no significant differences between the two groups for age, sex, heart failure aetiology, NYHA functional class or heart failure drug treatments. Additionally, no significant differences for markers of functional capacity or quality of life were observed at baseline between bicycle and NMS groups (Table 4.2).

Baseline assessments were performed on two separate occasions. To identify any effect of repeated exercise testing on subjects' performance, these two baseline assessments were analysed in the context of the post training results using a one-way ANOVA with post hoc Bonferroni analysis. Small increases were observed for 6-minute walk distance and treadmill exercise time between first and second baseline measurements that did not reach statistical significance (Figure 4.1). Peak VO_2 did not increase between the first and second baseline visits. The second baseline visit was used as the pre-training value for subsequent analyses.

Significant changes were observed following both forms of exercise training for markers of functional capacity (Table 4.2). Quality of life improved for the study group as a whole, as indicated by a lower score on the Minnesota questionnaire, but changes did not reach statistical significance when the training groups were examined independently. There was no significant change in peak VO_2 following the exercise programme in either training group.

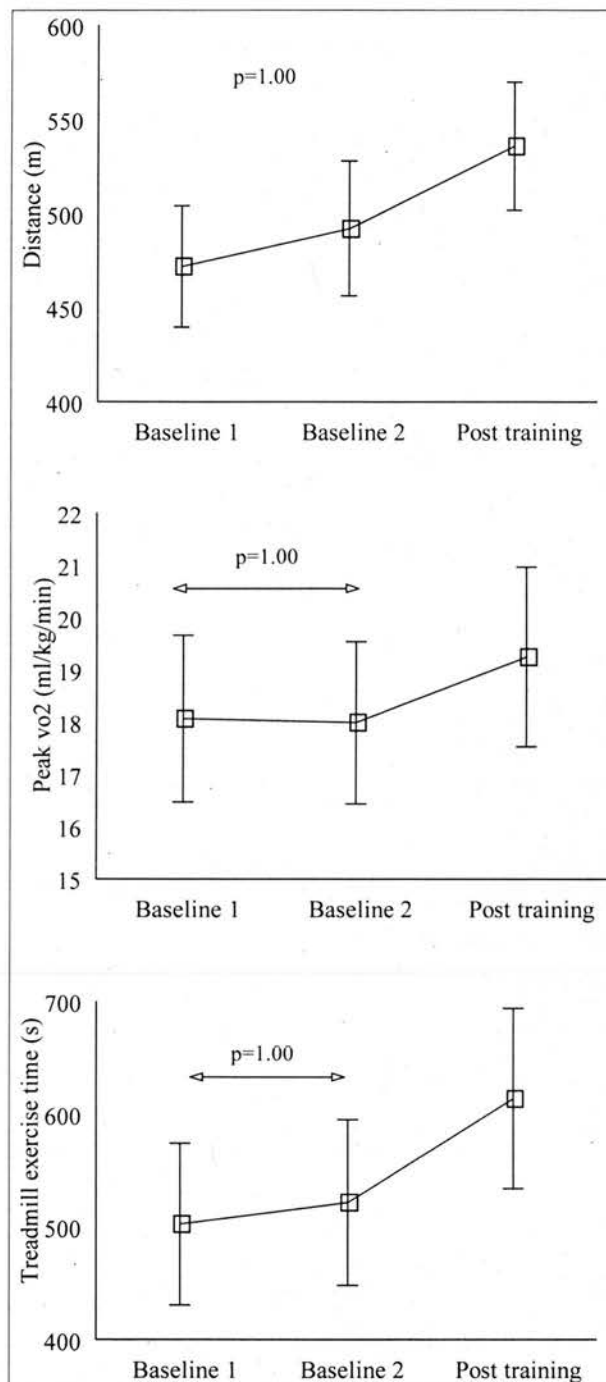


Figure 4.1. Mean exercise performance for whole group at baseline and post training (n=46).

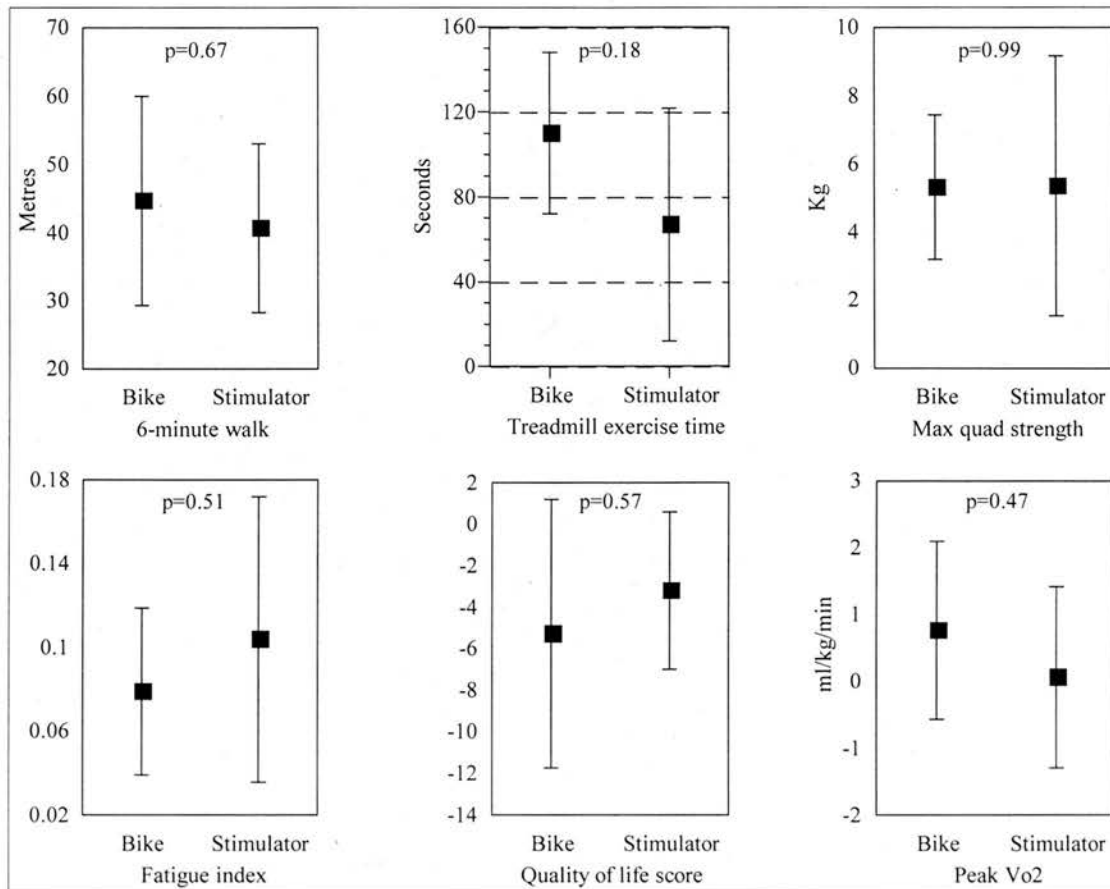


Figure 4.2. Mean absolute improvements in exercise variables and quality of life following training. Error bars indicate 95% confidence intervals; p values refer to differences in mean change between exercise groups.

The degree of change in indices of functional capacity observed following training was compared between the two groups. Figure 4.2 shows the mean absolute change in exercise capacity. Mean percentage increase in 6-minute walk was 10.3% (95%CI 6.59 to 14.1) for the bike group and 9.52% (95%CI 5.92 to 13.1) for the NMS group. Treadmill exercise time mean percentage increase was 33.0% (95%CI 10.8 to 55.3) for the bike group and 14.1% (95%CI 3.34 to 24.8) for the NMS group. Mean percentage increase in maximum quadriceps strength was 11.9% (95%CI 6.67 to 17.0) for the bike

group and 15.3% (95%CI 4.50 to 26.1) for the NMS group. Mean percentage improvement in fatigue index was 12.2% (95%CI 4.48 to 19.9) for the bike group and 17.2% (95%CI 5.40 to 29.1) for the NMS group. Mean percentage change in quality of life score was 2.47% (95%CI -28.8 to 33.8) for the bike group and -2.8% (95%CI -28.5 to 22.8) for the NMS group. Mean percentage increase in peak VO_2 was 5.5% (95%CI -1.48 to 12.5) for the bike group and 2.97% (95%CI -4.32 to 10.2) for the NMS group. There were no significant differences seen between bike and NMS groups in the degree of absolute or percentage change from baseline following training for any of the indices of exercise capacity or quality of life.

4.5 Discussion

The safety of exercise training for stable CHF patients delivered in a supervised environment is now well established (Belardinelli *et al.*, 1995a; Belardinelli *et al.*, 1999; Belardinelli *et al.*, 1995b; Dubach *et al.*, 1997a; Jette *et al.*, 1991; Wielenga *et al.*, 1999). There are also studies suggesting that it can be delivered at home safely and effectively (Adamopoulos *et al.*, 1993; Coats *et al.*, 1992; Hambrecht *et al.*, 1995; Hambrecht *et al.*, 2000a). These studies have demonstrated significant benefits for a variety of outcome measures including exercise capacity and quality of life and there is now preliminary evidence that prolonged training may have favourable effects on admission rates and mortality (Belardinelli *et al.*, 1999; Piepoli *et al.*, 2004). Recent guideline documents have therefore recommended an exercise training programme as part of the comprehensive rehabilitation and management of patients with chronic heart failure (Hunt *et al.*, 2001; Remme and Swedberg, 2002; Scottish Intercollegiate Guidelines

Network, 2002; Working Group on Cardiac Rehabilitation & Exercise Physiology and Working Group on Heart Failure of the European Society of Cardiology, 2001) and there is a need to examine new ways to deliver exercise therapy to patients in the community without the need for intense supervision.

This is the first randomised trial comparing NMS and conventional exercise training in a group of stable chronic heart failure patients. We have demonstrated that NMS is well tolerated, safe and results in significant improvement in markers of functional capacity. There was improvement in quality of life for both groups when examined together and a trend towards improved quality of life when NMS and bicycle groups were examined separately. NMS appeared to produce similar improvements in exercise capacity as bicycle training for the patients participating in our study and is a potentially attractive form of therapy since it requires less motivation and can be performed whilst a subject is sedentary. As such, it may be suitable for those patients who are either unwilling or unable to perform more conventional forms of exercise. Conventional training and NMS training are different, however. More muscle groups are utilised in conventional exercise regimes and there are significant changes in central haemodynamic variables during conventional exercise. Electrical muscle stimulation targets a smaller number of muscle groups and I did not identify any significant change in haemodynamic variables during periods of stimulation in five CHF patients. Although only a crude assessment of central response to local muscle stimulation, it is in keeping with other investigators who have identified no change in cardiac output (Maillefert *et al.*, 1998) and only small changes in heart rate during periods of NMS (Quittan *et al.*, 1999a). Whilst this supports the safety

of this form of muscle training in CHF patients, further work to investigate both central and local haemodynamic effects of muscle stimulation in a heart failure population is required. Physical inactivity itself is a risk factor for cardiovascular disease and the potential long-term benefits of training with NMS may be offset by this risk if it is the only form of training undertaken, although NMS may be of benefit in combination with conventional exercise or as a bridging therapy until a patient regains sufficient functional capacity to exercise conventionally. Formal tests of equivalence need to be performed in a larger trial to confirm that NMS is as effective as conventional exercise.

Peripheral muscle is abnormal in heart failure patients, with atrophy of both type I and type II muscle fibres (Lipkin *et al.*, 1988) and an apparent switch in fibre-type proportion to the less fatigue resistant fast-twitch type IIB fibres (Magnusson *et al.*, 1996). The quantity of aerobic enzymes and the density of mitochondria are reduced consistent with a decreased capacity for aerobic metabolism (Drexler *et al.*, 1992b). As such, the peripheral muscle is weaker with a decreased mass, reduced aerobic capacity and increased susceptibility to fatigue. Chronic low frequency NMS, such as used in our study, has previously been shown to produce an increase in oxidative capacity with reduced fatigability but little improvement in muscle strength (Badylak *et al.*, 1990; Maillefert *et al.*, 1998). Higher frequency intermittent protocols are recognised to retain fatigue resistance by improving aerobic capacity while also improving muscle strength (Pournezam *et al.*, 1988; Quittan *et al.*, 2001). The frequency and pulse duration of NMS protocols may be important in determining the profile of changes obtained with training and the use of a higher frequency protocol preferentially targeting type II fibres might

account for more marked improvements in muscle strength compared with improvements in fatigability. It is possible that in our study NMS training induced improvements due to a partial reversal of the unfavourable fibre type distribution and increased aerobic capacity but future studies with muscle biopsy before and after NMS training are required to test this theory.

Peak VO_2 did not improve following training in contrast to other studies (Adamopoulos *et al.*, 1993; Belardinelli *et al.*, 1999; Coats *et al.*, 1992; Dubach *et al.*, 1997a; Jette *et al.*, 1991; Wielenga *et al.*, 1999). The training period was short and of low intensity for both groups and this may account for the lack of change in peak VO_2 . Verbal reports from subjects were consistent with their training diaries, indicating compliance with the training programme. Unfortunately, with home-based programmes it is difficult to be absolutely certain about patient compliance and it is possible that poor compliance could have been partly responsible for the lack of change in peak VO_2 . Compliance with a prescription for exercise is an important issue for both clinical trials and clinical practice and exercise regimes that are poorly tolerated during a trial are unlikely to be better tolerated in practice. Future studies focussing on compliance with home-based training regimes are required to investigate this area further. In the context of this trial, however, functional improvement as determined by 6-minute walk, treadmill exercise time and muscle strength and fatigability did occur, and this is important given that many patients with chronic heart failure will be unwilling or unable to undertake more intensive forms of training. In addition, we did observe an improvement in perceived quality of life when the groups were considered together and this is also an important consideration in

patients with chronic symptoms and poor prognosis. Patients with the most severe symptoms may even be prepared to trade duration of life for quality (Lewis *et al.*, 2001) and whilst the effects of exercise training on prognosis remain to be fully established, improved quality of life remains a strong reason to recommend exercise therapy for selected patients. Peak VO_2 is a marker of prognosis in heart failure, however (Likoff *et al.*, 1987), and whilst low-intensity training may improve other markers of functional capacity or quality of life, lack of improvement in peak VO_2 suggests that prognosis may remain poor for these patients.

4.5.1 Conclusions

Exercise therapy reverses some of the peripheral changes seen in chronic heart failure and improves muscle strength, exercise time and perceived quality of life. Neuromuscular stimulation of the lower limbs is effective at improving functional capacity and could be offered in the future as an alternative to conventional training as part of a community based exercise training programme depending upon the results of future studies.

5 Study 2. Effect of exercise training on body composition in patients with chronic heart failure.

5.1 Abstract

5.1.1 Aims

Chronic heart failure is associated with skeletal muscle atrophy and weight loss. Skeletal muscle mass and peak oxygen uptake are important predictors of functional status and outcome in patients with stable chronic heart failure. Exercise training may potentially reverse some of these changes. This study was designed to assess changes in skeletal muscle mass and peak oxygen uptake following conventional exercise and neuromuscular stimulation of the legs.

5.1.2 Methods

36 patients with moderate stable chronic heart failure were randomly allocated to either a bicycle ergometer (bike) or neuromuscular stimulators (NMS) applied to quadriceps and gastrocnemius muscles to be used daily for six weeks. Assessment of patients before and after training included symptom-limited cardiopulmonary exercise test, quadriceps strength and fatigue resistance, 6-minute walk distance and dual-energy X-ray absorptiometry (DEXA) scanning.

5.1.3 Results

Both types of exercise training resulted in similar improvements in treadmill exercise time, leg strength and 6-minute walk test. Bike training resulted in a slightly greater mean increase in peak oxygen uptake per kilogram of lean muscle mass (Bike 7.5 (11.8) vs. NMS 4.7 (10.4) ml/min/kg, $p=0.45$). Despite significant improvements in functional capacity, there were no significant changes in body composition for total skeletal muscle mass, leg muscle mass or total body fat content. Lean muscle mass was strongly predictive of maximum oxygen uptake at baseline ($r=0.69$, $p<0.001$) and after exercise training ($r=0.63$, $p<0.001$).

5.1.4 Conclusions

This study suggests that in stable chronic heart failure, exercise training using bicycle ergometer or NMS results in favourable qualitative rather than quantitative changes in skeletal muscle. Correction of maximum oxygen uptake for skeletal muscle mass rather than total body mass is a more sensitive measure of changes associated with exercise training.

5.2 Introduction

Chronic heart failure is characterised by breathlessness, fatigue and poor exercise capacity. While circulatory insufficiency is the primary disorder it is now widely accepted that skeletal muscle in these patients has reduced strength and is more readily fatigued (Harrington *et al.*, 1997; Mancini *et al.*, 1992). A number of histological

abnormalities have been described in the skeletal muscle of chronic heart failure patients. A widely reported finding has been altered fibre type distribution with a change from slow twitch aerobic fibres to fast twitch glycolytic fibre types (Drexler *et al.*, 1992b; Lipkin *et al.*, 1988; Schaufelberger *et al.*, 1997; Sullivan *et al.*, 1990) although this has not been reported by all authors (Lindsay *et al.*, 1996). Molecular techniques have also suggested changes in myosin heavy chain proteins to faster glycolytic myosin types (Vescovo *et al.*, 1998). Reduced levels of metabolic enzymes involved in oxidative metabolism such as citrate synthase, succinate dehydrogenase and 3-hydroxyacyl CoA dehydrogenase have also been reported (Lindsay *et al.*, 1996; Mancini *et al.*, 1989; Mettauer *et al.*, 2001). Magnetic resonance techniques have demonstrated a reduced ability to replenish high energy phosphates, such as adenosine triphosphate (ATP), which appears to be a key metabolic abnormality (Broqvist *et al.*, 1992; Opasich *et al.*, 1996). The proposed mechanisms underlying these changes include reduced perfusion due to myocardial insufficiency, simple disuse atrophy and apoptosis induced by elevated local and circulating cytokines (Adamopoulos *et al.*, 1993; Vescovo *et al.*, 2001). A number of exercise training programmes have been shown to significantly improve functional capacity in CHF patients without significantly altering cardiac performance (Belardinelli *et al.*, 1995b; Coats *et al.*, 1992; Gordon *et al.*, 1996; Pu *et al.*, 2001). These studies have confirmed that although skeletal muscle has diminished function in CHF it can regain strength and power despite persistence of circulatory insufficiency.

Neuromuscular stimulation (NMS) differs from standard dynamic exercise training with respect to muscle group recruitment and cardiovascular responses to exertion but has

been shown to improve exercise performance in CHF patients (Maillefert *et al.*, 1998). This study aimed to examine whether NMS results in a distinctive change in the quality of skeletal muscle or whether an increase in muscle mass is responsible for the observed improvements in functional capacity. We therefore used dual energy x-ray absorptionometry before and after exercise training to examine changes in body composition and assessed the findings along with a detailed characterisation of functional status including cardiopulmonary exercise testing.

5.3 Methods

5.3.1 Study Population

Thirty-six patients with stable chronic heart failure, New York Heart Association (NYHA) class II to III, were recruited as described in section 3.1.1. Written informed consent was obtained from all subjects and the local research ethics committee approved the protocol. A series of age-matched men and women (9 female, 11 males) from the local population with no history of cardiac disease or other co-morbidity were included as a comparison group (Table 5.1, n=20).

5.3.2 Exercise-training regimes

Patients were randomised as described in section 3.4.1 to a training regime of either conventional bicycle training or NMS as described in sections 3.4.2 and 3.4.3. Patients underwent training 30 minutes per day, 5 days per week, for 6 weeks.

5.3.3 Patient assessment

Prior to randomisation, patients underwent baseline testing on two separate occasions at least 24 hours apart. The second baseline test used as the true baseline. Patients underwent 6-minute walk test (section 3.3.2), cardiopulmonary treadmill exercise test (section 3.3.4), and quadriceps strength and fatigue testing (section 3.3.3).

DEXA scanning was performed at one of the baseline visits and again after the end of the training period, as described in section 3.3.5. Results are expressed as mean values from two scans obtained on the same day using *Hologic Software* version 11.1 thus improving the overall precision of detecting a change between two time points. Whole

	Bike n=19	NMS n=17	Controls (n= 20)	p value (t-test, *ANOVA), ** Fishers exact)
Age (years)	60.7 ± 2.6	63.9 ± 2.6	61.4 ± 4.7	0.39*
Sex (Male: female)	15:4	12:5	11:9	0.39*
NYHA class (II, III)	14,5	14,3	0,0	0.70*
Aetiology of CHF (n)				
<i>Ischaemic</i>	12	9	-	0.73**
<i>DCM</i>	7	8	-	
Medication (%)				
<i>ACEI</i>	95	100	-	0.68
<i>Diuretic</i>	74	82	-	
<i>Digoxin</i>	47	41	-	
<i>Beta blocker</i>	37	41	-	
Ejection fraction (%)	32.4 ± 2.7	28.7 ± 1.7	-	0.24

Table 5.1. Baseline patient characteristics.

body densitometry was used to calculate fat free mass, skeletal muscle mass and total body bone mineral density.

5.3.4 Statistical analysis

Data analysis was performed using *SPSS for Windows*, version 13 as described in section 3.6. A paired *t*-test and one way ANOVA were used to compare data with a normal distribution, a Mann-Whitney U test was used to compare data with uneven distribution. Data are presented as mean \pm standard deviation (SD) unless otherwise stated. Correlations are expressed as univariate analyses and include 95% confidence intervals (95% CI). The Chi-square test was also used to compare groups. Significance was accepted at the 5% level ($p < 0.05$).

5.4 Results

The clinical characteristics of patients and controls are summarised in Table 5.1. Exercise groups were well matched for a range of clinical features. Healthy controls were also well matched for age.

	Bike (n=19)		NMS (n=17)		p value [§]
	Baseline	After training	Baseline	After training	
Peak VO ₂ (ml/kg/min) (kg=total body mass)	18.3 ± 5.1	19.8 ± 5.1	17.7 ± 4.9	18.6 ± 4.7	0.60
Peak VO ₂ (ml/kg/min) (kg=lean muscle mass)	49.5 ± 14.7	57.2 ± 13.6*	48.6 ± 15.4	54.0 ± 14.1	0.45
Treadmill exercise time (s)	520 ± 279	654 ± 271**	508 ± 201	568 ± 231*	0.35
6-minute walk (m)	480 ± 109	540 ± 109**	486 ± 115	531 ± 112**	0.68
Max quad strength (kg)	48.1 ± 13.7	54.1 ± 15.3**	42.2 ± 10.9	47.7 ± 12.8**	0.40
Quadriceps fatigue index	0.77 ± 0.14	0.84 ± 0.13**	0.77 ± 0.12	0.87 ± 0.1**	0.50
Minnesota QoL score	39.0 ± 21.0	31.0 ± 17.2	29.4 ± 20.4	25.5 ± 20.6	0.15
Total skeletal muscle (kg)	30.2 ± 4.9	30.6 ± 5.1	26.4 ± 4.8	25.8 ± 4.6	0.39
Body fat (%)	30.1 ± 6.7	30.0 ± 7.1	27.6 ± 5.5	28.0 ± 5.6	0.29

* p<0.05, ** p<0.01, comparing before and after training
[§] p- value for comparison of mean change between exercise groups

Table 5.2. Change in functional assessment and body composition after training.

There were no significant differences observed in the body composition of male and female CHF patients at baseline compared with age matched healthy controls for body fat, lean muscle mass and leg muscle mass (Table 5.3). There were similar improvements in treadmill exercise time, 6MW test, quadriceps muscle strength and fatigue resistance index in both exercise groups (Table 5.2). Correcting absolute oxygen uptake values for total body weight, there was no significant change in peak oxygen uptake (peak VO_2) in either group following training (bike 19.4 ± 1.4 to 19.8 ± 1.4 ml/kg/min, $p=0.64$, NMS 18.8 ± 1.6 to 18.5 ± 1.4 ml/kg/min, $p=0.80$). However, when values for oxygen uptake were recalculated using lean body mass (and not total body mass) there was a significant increase in peak VO_2 in the bike group (49.5 ± 14.7 to 57.2 ± 13.6 ml/kg/min, $p=0.01$) and a trend for an increase in the NMS group (48.6 ± 15.4 to 54.0 ± 14.1 ml/kg/min, $p=0.06$). There were no significant changes in total body skeletal

	CHF patients		Controls		p - value (ANOVA)
	Male (n=26)	Female (n=9)	Male (n=11)	Female (n=9)	
Body weight (kg)	82.9 ± 12.2	68.4 ± 15.8	86.1 ± 17.5	72.2 ± 8.4	0.23
Body mass index	27.2 ± 3.6	28.3 ± 4.7	28.3 ± 5.4	28.1 ± 3.4	0.67
Total lean mass (kg)	57.5 ± 7.7	44.4 ± 6.5	59.7 ± 6.9	42.6 ± 4.9	0.33
Total skeletal muscle mass (kg)	29.7 ± 4.4	22.1 ± 3.7	31.8 ± 3.8	24.6 ± 3.9	0.33
Leg skeletal muscle mass (kg)	17.7 ± 2.0	13.3 ± 2.5	18.9 ± 1.9	14.3 ± 2.2	0.41
Body fat (% body mass)	27.2 ± 4.7	36.7 ± 7.3	23.4 ± 6.8	39.5 ± 7.9	0.12
Bone mineral density (g/cm ³)	1.11 ± 0.12	0.98 ± 0.06	1.14 ± 0.05	1.00 ± 0.10	0.37

Table 5.3. Baseline body composition: male and female CHF patients and controls.

muscle mass or leg muscle mass and no significant change in total body fat after the period of exercise training in either training group or when all CHF patients were analysed together. There was no significant change in bone mineral density in either group (Table 5.2) or when all patients ($n=36$) were considered together (1.072 ± 0.025 to 1.077 ± 0.026 g/cm³, $p=0.25$).

At baseline, total body weight was not related to peak VO₂ ($r=-0.27$, $p=0.71$) but was more closely linked with peak VO₂ after exercise training ($r=0.67$, $p=0.02$). Peak VO₂ expressed as a percentage of age predicted VO₂ was slightly lower in the bike group at baseline and improved by only 4% after training while the NMS group started slightly higher and demonstrated only a 1.5% improvement. Peak VO₂ was strongly associated with lean body mass (Figure 5.1) both before ($r=0.69$, 95% CI 0.46 to 0.83) and after ($r=0.63$, 95% CI 0.35 to 0.71) exercise training for all CHF patients. There was no clear

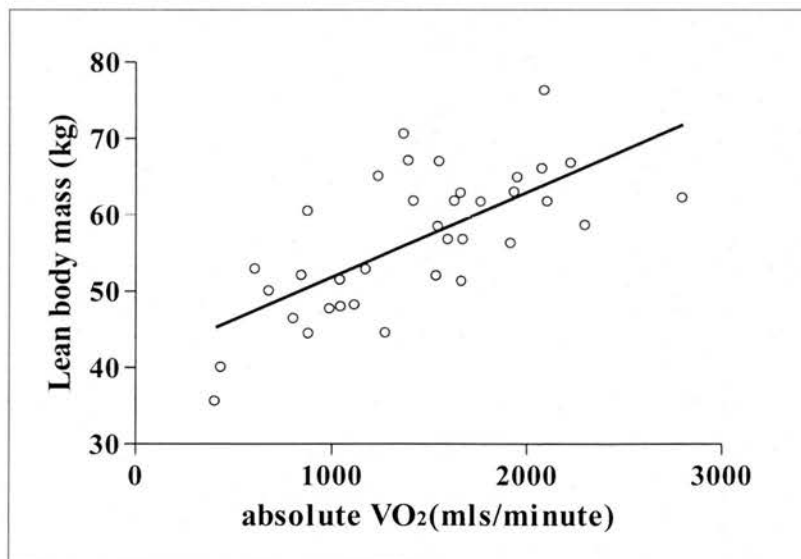


Figure 5.1. Association between lean body mass and absolute VO₂ at baseline. $r=0.69$, $p<0.001$.

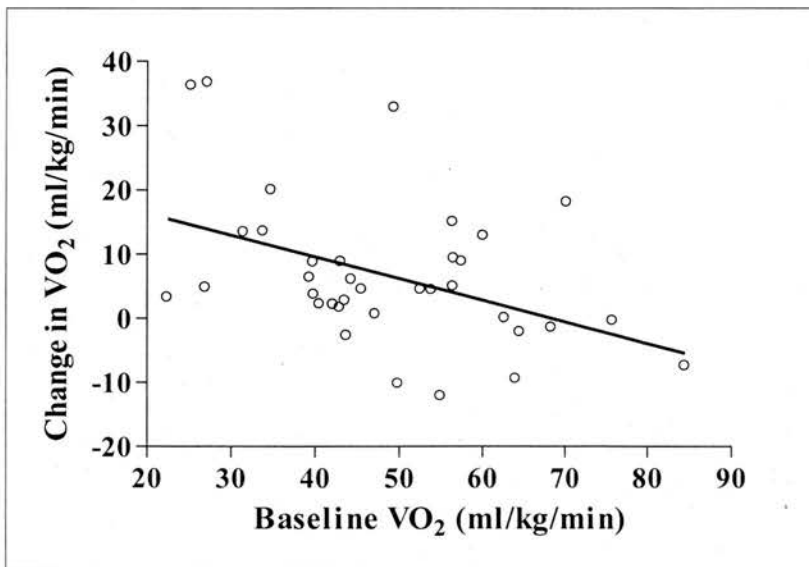


Figure 5.2. Relation between baseline peak VO₂ and increase in VO₂ (corrected for lean body mass). $r=-.43$, $p=0.01$, CI -0.67 to -0.12.

relationship between improvements in peak VO₂ and improvements in quadriceps muscle strength ($r=0.11$) or fatigue resistance ($r=0.05$). There was a negative association between baseline peak VO₂ and the absolute change in peak VO₂ (Figure 5.2) suggesting that patients with lowest baseline peak oxygen uptake had a greater increase in peak VO₂ following exercise training. Improvements in 6MW test were not associated with improvements in peak VO₂ ($r=0.17$, 95% CI -0.13 to 0.44) but peak VO₂ was correlated with 6MW at baseline ($r = 0.53$, $p<0.001$, 95% CI 0.33 to 0.68) and this relation strengthened after training ($r = 0.60$, $p<0.001$, 95% CI 0.36 to 0.77).

5.5 Discussion

In this study, exercise training using static bicycle and neuromuscular stimulation in patients with chronic heart failure produced no measurable change in skeletal muscle

mass, body fat content or bone mineral density. However, there was clear evidence of improvements in quadriceps muscle strength and fatigue resistance, and significant improvements in treadmill exercise time, 6MW test and peak VO_2 (corrected for skeletal muscle mass). In addition, in CHF patients we demonstrated that lean body mass was closely associated with peak VO_2 (expressed per unit lean muscle mass) at baseline but that the increase in peak VO_2 resulting from training was greatest in those patients with the lowest baseline peak oxygen uptake. These findings suggest that exercise training can result in significant improvements in functional capacity without increasing muscle mass. Furthermore they confirm the close link between two important prognostic markers in patients with CHF, namely, peak oxygen uptake and skeletal muscle mass (Anker *et al.*, 1997b; Anker *et al.*, 2003; Stelken *et al.*, 1996). This suggests that even patients with low baseline functional status and low skeletal muscle mass are able to benefit from exercise training. The question remains unanswered as to whether improvements in either of these parameters, muscle mass or peak VO_2 , by exercise training could alter mortality. There has been only one previous study suggesting that exercise training can improve prognosis (Belardinelli *et al.*, 1999) although a more recent meta-analysis of 9 studies has also supported this possibility (Piepoli *et al.*, 2004). Our study would suggest that at least short term exercise training will improve oxygen uptake but that this can occur without a concomitant increase in total skeletal muscle mass, suggesting the potential for the uncoupling of these two factors. Furthermore, it confirms the findings of other groups that patients with low baseline peak VO_2 can gain more from exercise training (Hambrecht *et al.*, 1995) and could therefore potentially achieve more prognostic benefit compared with CHF patients with higher baseline VO_2 .

Bicycle training resulted in significant improvements in VO_2 in keeping with a greater haemodynamic response to this form of training. NMS resulted in a smaller increase in VO_2 of borderline significance. I was able to detect a change in peak VO_2 by expressing absolute oxygen uptake per kilogram of skeletal mass but there was no significant difference when this was expressed using total body mass. The reason for this difference is likely to relate to the accuracy of the DEXA scan in measuring the tissue contributing greatest to oxygen consumption during exercise, namely skeletal muscle mass. Since we demonstrated a strong relationship between muscle mass and peak VO_2 both at baseline and after training (Figure 5.1), while total body mass was only related to peak VO_2 after training, correction of VO_2 to muscle mass is clearly a more sensitive way to detect change in oxygen consumption following training. This way of describing peak VO_2 is not widely used mainly because accurate measurement of lean body mass is only possible with DEXA or magnetic resonance imaging. Other workers have suggested this as a more accurate way of assessing cardiopulmonary function (Cicoira *et al.*, 2001) and there is some evidence that it may also have stronger prognostic value (Cicoira *et al.*, 2004). Bicycle training is more likely to result in improvement in peak VO_2 compared with NMS because of the larger muscle groups recruited, such as gluteus maximus and rectus femoris. While there was no statistically significant differences in functional capacity between the two forms of training, bicycle training did result in slightly greater improvements in 6MW test and treadmill exercise time. This is likely to be a reflection of the greater improvement in peak VO_2 in the bike group since we did see a relationship between improvements in peak VO_2 and 6-minute walk test. The muscle-specific assessments of function such as quadriceps strength and fatigue resistance, demonstrated

very similar improvements for Bike and NMS. The patients in this study had a wide range of functional capacity at baseline, with most patients in NYHA class II and some having a peak VO_2 close to that predicted for their age. Such patients are less likely to increase peak VO_2 after exercise training and may also partly explain why we did not see a significant improvement in this parameter when corrected for total body weight.

Since there was no significant change in body or leg muscle mass, the predominant change responsible for improved functional capacity must be related to changes in the quality of existing skeletal muscle. This further supports the notion of adaptability of skeletal muscle despite persistent circulatory insufficiency in CHF. Previous studies both in humans and in numerous animal models have demonstrated qualitative improvements in oxidative metabolism and high energy phosphate supplies (Adamopoulos *et al.*, 1993) resulting from exercise training in heart failure. Our findings suggest that NMS may also be able to influence these processes but possibly to a lesser degree than bicycle training. A limitation of this study is that it includes younger CHF patients than are typical of a heart failure population. This may partly explain why our patients had a slightly higher peak VO_2 than that reported in other similar studies (Stelken *et al.*, 1996). Further large trials including more elderly patients would be needed to confirm our findings.

One additional important finding is that despite the potential risk of extended rest while using the NMS there was no significant reduction in bone mineral density in patients randomised to this treatment modality. This is probably related to the short duration of daily use and improved activity levels in all patients during the study period as reflected by the improvements in functional performance.

Conclusions

This is the first study using DEXA scanning to follow-up heart failure patients that have undergone an exercise training programme. The lack of change in body composition observed in our study could reflect the short time period for training, the relatively low intensity home-based programme and the small number of patients included. However, the clear improvement in functional capacity observed for both forms of exercise, despite no increase in muscle mass, confirms the ability of skeletal muscle to undergo qualitative adaptation during exercise training in CHF.

6 Study 3. Change in circulating cytokines following two forms of exercise training in chronic stable heart failure.

6.1 Abstract

6.1.1 Background

A pro-inflammatory state is recognised in chronic heart failure and the degree of immune activation corresponds to disease severity and prognosis. Training is known to improve symptoms in heart failure but less is known about the effects of specific forms of training on the pro-inflammatory state.

6.1.2 Methods

46 patients with stable chronic heart failure underwent a home-based programme of exercise training for 30 minutes a day, 5 days per week over a 6-week period. 24 used a bicycle ergometer and 22 used an electrical muscle stimulator applied to quadriceps and gastrocnemius muscles. Tumour necrosis factor α (TNF α), TNF α soluble receptors 1 and 2, interleukin 6 and high sensitivity C-reactive protein were measured before and after the training period.

6.1.3 Results

Significant improvements in markers of exercise performance were seen in both training groups. Soluble TNF α receptor 2 levels decreased following training in the bike group

only (2900 ± 1069 pg/ml to 2625 ± 821 pg/ml, $p=0.013$). Trends towards a decrease in levels of TNF α and soluble TNF α receptor 1 were also seen in the bike group only. No change in circulating inflammatory markers was observed following stimulator training.

6.1.4 Conclusions

Physical training improves exercise capacity for patients with chronic heart failure but degree of attenuation of the pro-inflammatory response may depend on the mode of training despite similar improvements in exercise capacity.

6.2 Introduction

It is no longer accepted that heart failure is a syndrome solely dependent on the degree of left ventricular systolic dysfunction. Pump inefficiency is a trigger for maladaptive neurohormonal responses and endothelial dysfunction and despite modern pharmacological treatments, heart failure continues to carry a high morbidity and mortality (Cowie *et al.*, 1997). Attention has therefore been directed towards other possible mechanisms that may be responsible for disease progression and symptom generation.

There is evidence of a state of heightened immune activation in chronic heart failure. Pro-inflammatory cytokines interleukin 2 (IL-2) (Matsumori *et al.*, 1994), interleukin 6 (IL-6) (Munger *et al.*, 1996) and tumour necrosis factor α (TNF α) (Levine *et al.*, 1990; Torre-Amione *et al.*, 1996a) are found in higher concentrations in the circulation of heart failure patients compared with normal subjects and some reports demonstrate

association between increased concentrations of cytokines and disease severity (Levine *et al.*, 1990; Torre-Amione *et al.*, 1996a). The reason for the heightened immune response in heart failure is not clear although possibilities include tissue hypoxia (Hasper *et al.*, 1998; Leeper-Woodford and Detmer, 1999; Matsui *et al.*, 1999), myocardial production (Kapadia *et al.*, 1997; Torre-Amione *et al.*, 1996b) and endotoxin-mediated stimulation following bacterial translocation across an oedematous gut wall (Anker *et al.*, 1997a; Niebauer *et al.*, 1999). It is most likely, however, that there is a diffuse source of cytokine activation and activation of the immune response may involve different pathways for different individuals.

Exercise training can partially reverse skeletal muscle abnormalities observed in heart failure and improves symptoms (Adamopoulos *et al.*, 1993; Belardinelli *et al.*, 1999; Coats *et al.*, 1992; Hambrecht *et al.*, 1997; Magnusson *et al.*, 1996; Sullivan *et al.*, 1991; Wielenga *et al.*, 1999) but the optimal form of exercise training and the effect of training on the inflammatory response remains unclear. Additionally, the influence of different forms of physical training on cytokine expression has not been established. As such, this study was designed to explore the relationship between the pro-inflammatory cytokines IL-6, TNF α , the two soluble receptors for TNF α , sTNFr1 and sTNFr2, and the inflammatory marker C-reactive protein (CRP), with exercise performance. The changes in these inflammatory markers following a home-based programme of either bicycle exercise training or neuromuscular stimulation of the legs was also evaluated.

6.3 Methods

6.3.1 Study Population

46 subjects with stable chronic heart failure and New York Heart Association (NYHA) class II-III symptoms were recruited as described in section 3.1.1. Baseline characteristics are shown in Table 6.1. All subjects were on appropriate medical therapy that included angiotensin converting enzyme inhibitors (ACEi), diuretic, aldosterone antagonist, digoxin or beta-blockers. None of the subjects were participating in a specific exercise programme prior to inclusion in the study. Exclusion criteria outlined in section 3.1.1 applied. None of the subjects taking part in the study was known to have any intercurrent infective or malignant disease. One subject did not complete the exercise training programme due to back discomfort. All patients randomised were included in the final analysis.

	n=46
Age, years	62 ± 10.3
Sex, male, n (%)	38 (83)
CHF aetiology, IHD / DCM, n (%)	29 / 17 (63 / 37)
NYHA Functional class, II / III, n (%)	35 / 11 (76 / 24)
Ejection fraction, %	30.0 ± 7.9
Medications, n (%)	
<i>ACE-inhibitor</i>	45 (98)
<i>Diuretic</i>	37 (80)
<i>Digoxin</i>	21 (46)
<i>Beta-blocker</i>	18 (39)
<i>Spironolactone</i>	4 (9)

Table 6.1. Patient characteristics.

Written informed consent was obtained from all subjects prior to randomisation and the protocol was approved by the local research ethics committee.

6.3.2 Patient assessment

Subjects underwent assessment on three occasions. Two baseline assessments were performed at least 24 hours apart prior to randomisation and one assessment was performed following the exercise training period. At each visit subjects performed a 6-minute walk test (section 3.3.2), a symptom-limited cardiopulmonary treadmill exercise test (section 3.3.4) and an isometric quadriceps strength and fatigue test (section 3.3.3). Data from the second baseline assessment were used as the true baseline.

At one of the baseline visits and following the training period each patient completed a Minnesota 'living with heart failure' quality of life questionnaire (section 3.3.8).

6.3.3 Cytokine analyses

Venous blood was collected at one of the baseline visits and after the end of the 6-week training period, as described in section 3.3.6 for analysis of $\text{TNF}\alpha$, sTNF_{r1} , sTNF_{r2} , IL-6 and hs-CRP.

6.3.4 Exercise training

Following baseline assessment, subjects were randomised to receive either a recumbent bicycle ergometer or a neuromuscular stimulator for home use 30 minutes per day, five days per week over a 6-week training period, as described in section 3.4.

6.3.5 Statistical Analyses

Data were analysed using *SPSS for Windows* version 13 as described in section 3.6. Data are presented as mean \pm standard deviation unless otherwise stated. Normally distributed paired data were analysed using the paired *t*-test. Paired data that were not normally distributed were analysed using the Mann Whitney U test where appropriate. Correlations between variables were calculated using the Pearsons bivariate correlation test for normally distributed data and the Kendall tau-b test for non-normally distributed data. A p value of <0.05 was considered statistically significant.

6.4 Results

Improvements in 6-minute walk test distance, treadmill exercise time, maximal quadriceps leg strength and quadriceps fatigue index were observed in the group as a whole and when the groups were examined separately (Table 6.2). One-way analysis of

	Whole group (n=46)		Bike group (n=24)		NMS (n=22)	
	Mean change	p-value	Mean change	p-value	Mean change	p-value
6MW (m)	42.7 \pm 30.7	<0.001	44.6 \pm 34.6	<0.001	40.6 \pm 26.5	<0.001
QoL	-4.29 \pm 11.8	0.02	-5.27 \pm 14.6	0.11	-3.20 \pm 8.11	0.090
Treadmill time(s)	90.1 \pm 101	<0.001	110 \pm 85.5	<0.001	66.8 \pm 114	0.020
Peak VO ₂ (ml/kg/min)	0.43 \pm 3.05	0.38	0.76 \pm 3.12	0.276	0.060 \pm 3.01	0.932
Max quad strength(kg)	5.33 \pm 6.54	<0.001	5.32 \pm 4.82	<0.001	5.35 \pm 8.16	0.009
Fatigue index	0.09 \pm 0.12	<0.001	0.079 \pm 0.090	0.001	0.10 \pm 0.15	0.005

Table 6.2. Mean changes in functional capacity following training.

variance indicated that the mode of exercise training was unimportant in determining the degree of change seen. Improvement in quality of life score following training was observed for the whole group ($p=0.02$) but not when the groups were considered separately. Increase in peak VO_2 following exercise training did not reach statistical significance for either training group.

Pre-training concentrations of circulating inflammatory markers are shown in Table 6.3. Although no normal control subjects were included in this study, levels of IL-6, $\text{TNF}\alpha$, sTNF_{r1} , sTNF_{r2} and hs-CRP are all elevated in comparison with the assay manufacturers' data and previously published data (Chenillot *et al.*, 2000; Herbeth *et al.*, 2001). No relationship between concentrations of individual inflammatory markers and NYHA functional class or left ventricular ejection fraction was observed. No significant changes were detected in circulating inflammatory markers following training in the study group as a whole although a trend towards lower levels of sTNF_{r2} was seen ($p=0.052$, Table 6.3). sTNF_{r2} levels decreased significantly in the bike training group ($p=0.013$) but not in the NMS group. Trends towards lower concentrations of $\text{TNF}\alpha$ and sTNF_{r1} were seen in the bike group but not in the NMS group. hs-CRP and IL-6 did not change significantly following training in the bike group and no changes for any inflammatory marker were observed in the NMS training group.

Correlations were seen at baseline between individual inflammatory markers (Table 6.4). A weak negative correlation was observed between IL-6 and treadmill exercise time (coefficient = -0.223, $p = 0.05$); $\text{TNF}\alpha$ correlated weakly with treadmill exercise time (coefficient = 0.242, $p = 0.037$). sTNF_{r1} correlated with age (coefficient = 0.277, p

= 0.016).

	Whole group (n=38)	Bike Group (n=20)	NMS Group (n=18)
hs-CRP (mg/L)			
Pre training	3.57 ± 2.7	3.67 ± 2.60	3.46 ± 2.9
Post training	4.90 ± 8.9	3.27 ± 3.64	6.64 ± 12.2
p-value	0.50	0.19	0.75
IL-6 (pg/ml)			
Pre training	9.82 ± 14.6	12.0 ± 18.6	7.41 ± 8.1
Post training	8.67 ± 15.4	11.7 ± 21.3	5.69 ± 4.6
p-value	0.68	0.54	0.96
TNF α (pg/ml)			
Pre training	8.43 ± 3.6	7.95 ± 3.33	8.94 ± 3.84
Post training	7.76 ± 2.8	6.90 ± 1.84	8.63 ± 3.40
p-value	0.16	0.17	0.50
sTNF $_{r1}$ (pg/ml)			
Pre training	1670 ± 760	1515 ± 648	1842 ± 853
Post training	1593 ± 701	1355 ± 534	1831 ± 782
p-value	0.56	0.16	0.44
sTNF $_{r2}$ (pg/ml)			
Pre training	3073 ± 1060	2900 ± 1069	3266 ± 1042
Post training	2900 ± 930	2625 ± 821	3175 ± 978
p-value	0.052	0.013	0.88

Table 6.3. Training-induced changes in circulating inflammatory markers.

Marker	Correlation Coefficient	p-value
IL-6 with		
sTNF $_{r1}$	0.397	<0.001
sTNF $_{r2}$	0.246	0.031
CRP	0.268	0.018
sTNF $_{r1}$ with		
sTNF $_{r2}$	0.690	<0.001
CRP	0.340	0.003
sTNF $_{r2}$ with		
CRP	0.320	0.005

Table 6.4. Relationship between inflammatory markers at baseline.

6.5 Discussion

Whilst the beneficial effects of physical training in chronic heart failure for markers of exercise performance (Belardinelli *et al.*, 1999; Coats *et al.*, 1992; Wielenga *et al.*, 1999), muscle metabolism (Adamopoulos *et al.*, 1993), endothelial function (Hambrecht *et al.*, 1998; Linke *et al.*, 2001) and perhaps prognosis (Belardinelli *et al.*, 1999) are documented, less is known about the effects of physical training on the pro-inflammatory state. Larsen *et al.* have demonstrated modest reductions in circulating TNF α following a 12-week training period (Larsen *et al.*, 2001) and Adamopoulos *et al.* have shown reduction in TNF α , soluble TNF α receptors 1 and 2, soluble IL-6 receptor and markers of apoptosis with correlations between cytokine reductions and improvements in markers of exercise performance (Adamopoulos *et al.*, 2002). This study confirms high levels of circulating pro-inflammatory cytokines in a group of patients with chronic heart failure although I did not demonstrate a convincing relationship between cytokine concentrations and severity of heart failure based on NYHA class or exercise performance. This may be due to the stability of symptoms for the whole study group and the small number of NYHA class III patients (11 subjects). I did not demonstrate a reduction in levels of circulating TNF α or IL-6 following training as other workers have done, although there was a trend towards lower circulating levels of sTNF $_{r2}$ following training in the whole study group. The fall in sTNF $_{r2}$ was significant in the bike training group only. A trend towards lower concentrations of TNF α and sTNF $_{r1}$ was seen in the bike training group although results did not reach statistical significance. The fact that TNF α , IL-6 and CRP did not change significantly could

reflect the sensitivity of these markers to short-term changes in immune state, for example, changes occurring with intercurrent infection or physical exertion and, as such, the relatively small population size in this study may limit the ability to resolve changes for these markers. The differential changes seen following stimulator and bike training need to be confirmed in a larger trial.

The existence of a heightened immune response in chronic heart failure is now accepted but its possible role in the pathogenesis of the heart failure syndrome is a subject for debate. Recent clinical trials have not shown benefit from treatments which target TNF α (Chung *et al.*, 2003; Mann *et al.*, 2004) and this has raised the possibility that elevated levels of circulating cytokines are markers of disease severity rather than causative agents. The results of these trials which target single cytokine pathways do not absolutely rule out a role for inflammation in the progression of heart failure, however. Certainly TNF α levels have been found to be elevated in patients with left ventricular systolic dysfunction (Levine *et al.*, 1990; Matsumori *et al.*, 1994), and in higher concentrations in those with more severe heart failure (Torre-Amione *et al.*, 1996a). Animal studies have demonstrated that TNF α can depress myocardial contractility and induce cardiomyopathy (Bryant *et al.*, 1998; Finkel *et al.*, 1992; Hegewisch *et al.*, 1990), and cytokines including TNF α can promote over-expression of inducible nitric oxide synthase (iNOS) (Forstermann *et al.*, 1994) which may cause elevated levels of intracellular nitric oxide sufficient to depress oxidative capacity and myocardial function. Additionally, cytokines including TNF α are stimulators of apoptotic cell death (Ware *et al.*, 1996). IL-6 is elevated in chronic heart failure (Munger *et al.*, 1996) with higher

concentrations found in patients with more severe symptoms and left ventricular systolic dysfunction (Torre-Amione *et al.*, 1996a), and high concentrations have been linked to prognosis (Kell *et al.*, 2002; Tsutamoto *et al.*, 1998). The two receptors for the TNF α homotrimer, TNF r_1 and TNF r_2 , are widely expressed and mediate the actions of TNF α (Sack *et al.*, 2000) – the soluble forms of both subtypes which were measured in our study are found in the circulation in higher concentrations in chronic heart failure with concentration closely correlated with mortality (Deswal *et al.*, 2001; Ferrari *et al.*, 1995; Rauchhaus *et al.*, 2000). The precise role of the circulating TNF receptors is uncertain, however. Receptors are up-regulated on exposure to TNF α and shed into the circulation. The soluble receptors can bind to TNF α in the circulation and may buffer its action, either attenuating its bioavailability or, alternatively, acting as a reservoir of TNF α , thereby prolonging its normally short half-life (Aderka *et al.*, 1992). As such, concentrations of soluble TNF α receptors may reflect the overall level of TNF α exposure irrespective of whether the soluble receptors limit or potentiate TNF α bioactivity, and although TNF α levels may vary over time, soluble TNF α receptors may represent the overall state of immune activation. As such, the reduction in circulating levels of sTNF r_2 following training in the bike group may reflect a reduction in the overall state of immune activation.

In contrast, changes in circulating cytokine levels following training with neuromuscular stimulation were not observed, despite improvements in functional capacity in both training groups. Peak VO $_2$ did not increase following training for either group indicating either low intensity training regimes or poor patient compliance. Although patients

maintained exercise diaries, it is difficult to be absolutely certain of compliance with any home-based training programme and the lack of change in cytokine levels in the NMS group may have been due to poor compliance with this form of training. Alternatively, the absence of change in circulating inflammatory markers in the NMS group may be due to less muscle bulk having been exercised over the six-week period for those subjects in view of the likely more limited muscle recruitment by these devices compared with conventional bicycle exercise. Whilst changes in muscle structure promoting improved oxygen delivery following conventional training regimes have been studied in heart failure patients previously, with beneficial changes in capillary density (Scarpelli *et al.*, 1999), flow dependent flow (Hornig *et al.*, 1996) and peak leg blood flow (Sullivan *et al.*, 1988a), the long term effects of training with neuromuscular stimulation have not been studied. Additionally, the acute effect of exercise with electrical stimulation on muscle metabolism and deoxygenation in heart failure has not been investigated. We did not observe any acute increase in heart rate or blood pressure for five patients undergoing leg stimulation (data not shown), but further work examining the acute haemodynamic effects of NMS in a heart failure population is required. Since tissue hypoxia is a stimulus for TNF α production (Leeper-Woodford and Detmer, 1999; Matsui *et al.*, 1999) and the degree of oxygen delivery and tissue hypoxia both during exercise and following training may be different for conventional training regimes and electrical stimulation, there may be differing effects on inflammatory response. Further work clarifying the mechanisms by which the pro-inflammatory state is attenuated following different modes of physical training is required. Training regimes may have differing peripheral effects, which may result in differing functional outcomes.

If the pro-inflammatory state in heart failure is partly responsible for disease progression rather than merely a surrogate marker of disease severity, then the mode of exercise training chosen may be important in determining prognostic benefit despite similar changes in exercise performance.

Conclusions

Exercise training with both neuromuscular stimulation and conventional cycle ergometer results in beneficial changes in exercise performance in stable chronic heart failure patients. However, the pro-inflammatory state appears to be attenuated in a group receiving conventional training but not in a group receiving training with NMS. It will be important to identify the source of immune activation and the mechanisms by which training affects this inflammatory state, as it may be possible to tailor training regimes to produce maximal benefit both for symptoms of heart failure and perhaps also prognosis.

7 Study 4. Neuromuscular and conventional exercise training in stable and recently decompensated patients with chronic heart failure.

7.1 Abstract

7.1.1 Aims

Previous studies have highlighted the benefits of exercise training in stable chronic heart failure (CHF) but no data exist regarding patients with recently decompensated CHF. Poor effort tolerance and demotivation may be more pronounced in this patient group making delivery of conventional training difficult. We examined bicycle ergometer exercise and neuromuscular stimulation (NMS) in stable and recently decompensated groups.

7.1.2 Methods

15 patients, NYHA class II-III with stable CHF (S-CHF) and no admission within the preceding 3 months and 25 patients with recently decompensated CHF (RD-CHF) were recruited. NT-pro BNP, 6-minute walk (6MW), quadriceps strength and fatigue test and cardiopulmonary exercise test were assessed at baseline and after exercise training. Patients were randomised to either no exercise (control), bike or NMS exercise daily for 30 minutes five days per week for 6 weeks.

7.1.3 Results

In 23 patients completing the study, exercise training resulted in improvement in NYHA class (2.13 ± 0.352 to 1.87 ± 0.516 , $p=0.041$), 6MW (553 ± 131 to 569 ± 139 m, $p=0.046$), VO_2 at anaerobic threshold (AT, 12.6 ± 3.05 to 13.8 ± 3.10 ml/kg/min, $p=0.036$), OUES (oxygen uptake efficiency slope, 1.86 ± 0.699 to 2.11 ± 0.560 , $p=0.032$), VE/VCO₂ slope (NMS only, 30.1 ± 3.80 to 24.6 ± 3.89 , $p=0.043$), NT-pro BNP (1721 ± 1752 to 1209 ± 1248 pg/ml, $p=0.005$), quadriceps strength (34.2 ± 13.5 to 39.2 ± 16.0 kg, $p=0.002$) and treadmill exercise time (599 ± 207 to 683 ± 188 s ($p=0.002$)). NT-pro BNP fell significantly in the RD-CHF group receiving NMS training (2859 ± 2352 pg/ml to 1865 ± 1791 pg/ml, $p=0.043$) but not in the bike (1949 ± 1628 to 1086 ± 1369 pg/ml, $p=0.18$) or control group (1367 ± 1352 to 921 ± 1404 , $p=0.073$). No change in NT-pro BNP was seen in S-CHF patients. A trend for increased VO_2 at AT was seen in RD-CHF and S-CHF patients in NMS and bike groups but not controls.

7.1.4 Conclusions

For RD-CHF patients able to undertake an exercise programme, significant improvements in symptoms and functional capacity are observed. NMS appears to be effective in this group and could be a useful mode of delivery of exercise where conventional training is not practicable.

7.2 Introduction

The syndrome of chronic heart failure (CHF) due to left ventricular systolic dysfunction

is a complex interaction between poor cardiac output, neurohormonal maladaptations and chronic peripheral changes in skeletal muscle. Meta-analyses have identified the benefit of exercise training in improving morbidity, mortality and quality of life in patients predominantly with stable chronic heart failure (S-CHF) (Piepoli *et al.*, 2004; Rees *et al.*, 2004; van Tol *et al.*, 2006). These studies have also explored different modalities of training including dynamic and static regimens alone and in combination. More recently, neuromuscular electrical stimulation (NMS) has emerged as a training modality which may provide equivalent benefits to static bicycle training while being potentially better tolerated by a wider range of patients (Dobsak *et al.*, 2006; Nuhr *et al.*, 2004; Quittan *et al.*, 2001). However, a number of important issues remain poorly understood with regard to exercise training in heart failure. Firstly, patients included in previous exercise training studies appear to be highly selected on the basis of greater baseline physical fitness and motivation, hence they may not be truly representative of the spectrum of CHF patients seen in hospital and community practice. Secondly, patients with the most severe symptoms may have the most to gain from training but maintenance of an exercise training programme in this group is often difficult due to problems of motivation, comorbidities and limiting symptoms. As such, these patients have not been well studied. Thirdly, the ideal timing of an exercise training programme in the course of a patient's illness pathway is unknown, and in particular the safety and efficacy of exercise training in recently decompensated heart failure patients is unknown. We therefore sought to compare conventional bicycle ergometer exercise training with NMS of quadriceps / gastrocnemius muscles in a group of patients selected from a well defined hospital-based population with either stable heart failure (S-CHF) or

following a hospital admission with recently decompensated chronic heart failure (RD-CHF).

7.3 Methods

7.3.1 Patient selection

40 patients with NYHA class II to III symptoms of heart failure were recruited in a university teaching hospital setting. 15 of the patients were recruited from outpatient clinics and were classed as having stable chronic heart failure (S-CHF) as described in section 3.1.1. 25 patients were recruited following an admission with a primary diagnosis of recently decompensated chronic heart failure (RD-CHF), i.e. worsening and uncontrolled peripheral oedema or pulmonary oedema defined clinically and on chest radiograph, as described in section 3.1.2. RD-CHF patients were invited to participate in the study during their in-patient admission once they were deemed fit to provide informed consent. They were treated for decompensated heart failure with standard medical therapy and discharged from hospital once stable. They returned for initial physical assessment between 2 and 4 weeks post-discharge. All patients recruited had been previously diagnosed with heart failure on the basis of clinical assessment and documented left ventricular systolic dysfunction described as at least moderate in severity on echocardiography. Exclusion criteria outlined in section 3.1.2 applied. No subject was participating in any exercise training programme prior to recruitment. At the time of first baseline assessment, participating patients were on standard medical therapy that included angiotensin converting enzyme inhibitors (ACEi) or angiotensin 2 receptor

blockers (ARB), diuretic, aldosterone antagonists, digoxin or beta-blockers. Baseline characteristics for recruited patients are shown in Table 7.1. Written informed consent was obtained from all subjects prior to randomisation. The protocol was approved by the local research ethics committee and conformed with the principles outlined by the Declaration of Helsinki.

	Whole group	RD-CHF	S-CHF	<i>p</i>
n	40	25	15	
Age	63.8 ± 10.2	64.6 ± 11.8	62.3 ± 6.87	0.49
Sex Male:Female, n (%)	31:9 (78:22)	21:4 (84:16)	10:5 (67:33)	0.189
Aetiology ischaemic:non-ischaemic, n (%)	20:20 (50:50)	11:14 (44:56)	9:6 (60:40)	0.327
BP	124/75.3 ± 22.1/10.1	116/73.4 ± 17.7/11.6	134/77.4 ± 24.1/7.43	0.015 / 0.32
NYHA at baseline II:III, n (%)	33:7 (82:18)	19:6 (76:24)	14:1 (93:7)	0.162
Drugs n (%)				
Aspirin	18 (45)	12 (48)	6 (40)	0.622
ACEi / ARB	33 (83)	19 (76)	14 (93)	0.162
Beta-blocker	20 (50)	10 (40)	10 (67)	0.102
Loop diuretic	37 (92)	23 (92)	14 (93)	0.877
Spironolactone	18 (45)	13 (52)	5 (33)	0.251
Digoxin	27 (68)	17 (68)	10 (67)	0.931
Statin	21 (52)	11 (44)	10 (67)	0.165

Table 7.1. Baseline characteristics prior to randomisation.

7.3.2 Assessment

Subjects underwent assessment on four occasions. Two initial assessments were performed at least 24 hours apart prior to randomisation. Data from the first assessment were discarded and the second assessment data were used as baseline. A third assessment was performed within five days of the end of a 6-week training period. A final assessment was then made after a further 6-week period of “detraining” during which patients were neither encouraged nor discouraged from taking part in any form of physical training.

At each visit subjects performed a 6-minute walk test (6MW, section 3.3.2), a symptom-limited cardiopulmonary treadmill exercise test (section 3.3.4) and an isometric quadriceps strength and fatigue test (section 3.3.3). Blood was collected for N-terminal pro BNP (NT-pro BNP) analysis at baseline assessment and within five days of completing the exercise training programme using a standard assay (section 3.3.7, Roche Diagnostics, Basel, Switzerland).

7.3.3 Randomisation

Patients were randomised by an independent third party according to a pre-defined block schedule to one of three groups as discussed in section 3.4.1. Group A underwent the same performance assessment and follow-up as the two training groups but without any formal training programme. Group B underwent conventional cycle ergometer training as described below. Group C underwent training with NMS as described below.

7.3.4 Exercise training programmes

Following baseline assessment and randomisation, patients undertook a six-week programme of either usual activity (Group A), home-based cycle ergometer training (group B, bike) or home-based neuromuscular electrical stimulation of the quadriceps/gastrocnemius muscles of the legs (group C, NMS). Bike and NMS training regimes are discussed in detail in sections 3.4.2 and 3.4.3, respectively. Patients participating in all three groups were visited at home after two weeks and contacted by telephone after four weeks to monitor progress.

7.3.5 Statistical analysis

Data for randomised patients were analysed using *SPSS for Windows* version 13 on an intention to treat basis, as discussed in section 3.6. Data are presented as mean \pm standard deviation unless otherwise stated. Normally distributed paired data were analysed using the paired *t*-test. Paired data that were not normally distributed were analysed using the Mann Whitney U test where appropriate. Repeated measure data were analysed using one-way ANOVA with post hoc Bonferroni test. A *p* value of <0.05 was considered statistically significant.

7.4 Results

At baseline, S-CHF and RD-CHF groups were not significantly different for NYHA class, age, sex, CHF aetiology or drug use (Table 7.1). Drug dosages were not significantly different between groups (data not shown). Systolic BP was significantly

lower in the RD-CHF group.

7.4.1 Recently decompensated CHF vs. stable CHF groups

In total, from 40 patients initially recruited, 17 dropped out of the study. The majority of these were patients in the RD-CHF group (n=11). 6 patients (5 RD-CHF) dropped out during the baseline assessment phase prior to randomisation due to severity of symptoms and inability to complete the baseline performance assessments. 5 (4 RD-CHF patients) dropped out during the exercise programme – 3 from group B (Bike) and 2 from group C (NMS). A further 6 dropped out before the final assessment could be undertaken, 3 S-CHF and 3 RD-CHF. Dropout following randomisation was due to worsening of heart failure symptoms and no patient reported a specific intolerance of either exercise regime as a precipitating factor. One RD-CHF patient was readmitted due to worsening symptoms prior to the final visit.

Figure 7.1 and Figure 7.2 show changes observed following the training period for groups A, B and C when combined or separated between RD-CHF and S-CHF. NMS and BIKE patients show similar improvements in NT-pro BNP in the RD-CHF group only, with NMS (group C) reaching statistical significance (Figure 7.1). The small improvement observed in peak VO_2 at AT observed for NMS and Bike groups together (B and C combined) did not reach statistical significance when S-CHF and RD-CHF patients were analysed separately (Figure 7.2). No significant changes were observed in NYHA class, 6MW distance, treadmill exercise time, quadriceps strength and peak VO_2 when S-CHF and RD-CHF data were analysed separately (data not shown).

7.4.2 NMS vs bicycle regimes

Examining bicycle and NMS exercise modalities separately, NMS (group C) resulted in significant improvements in treadmill exercise time, quadriceps strength, NT-pro BNP and VE/VCO₂ slope as shown in Table 7.2 and Table 7.3. A trend for improvement in NYHA class, 6MW distance, treadmill exercise time and quadriceps strength was observed in the bike training group (B). No change in peak VO₂ or VO₂ at AT was observed following training for either groups B or C.

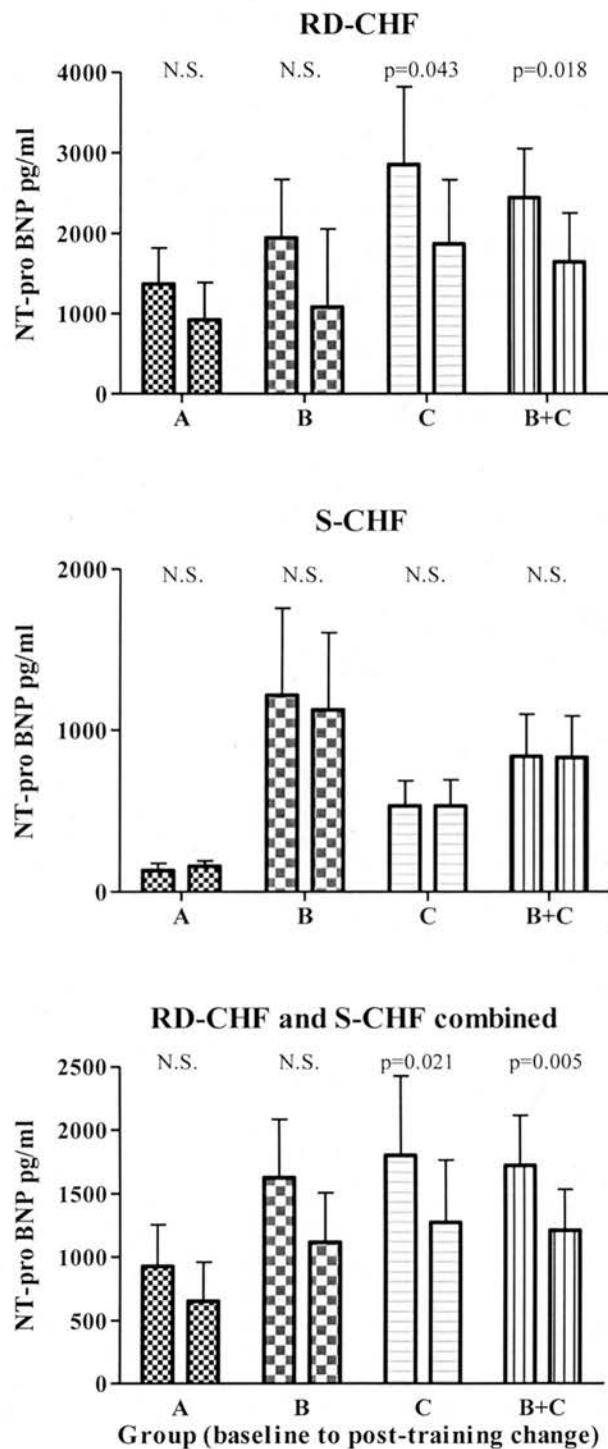


Figure 7.1. NT pro BNP between baseline and after training for control and exercising groups. A, control group; B, bike group; C, NMS group, B+C, all exercising. RD-CHF, recently decompensated patients; S-CHF, stable patients only. N.S., not significant.

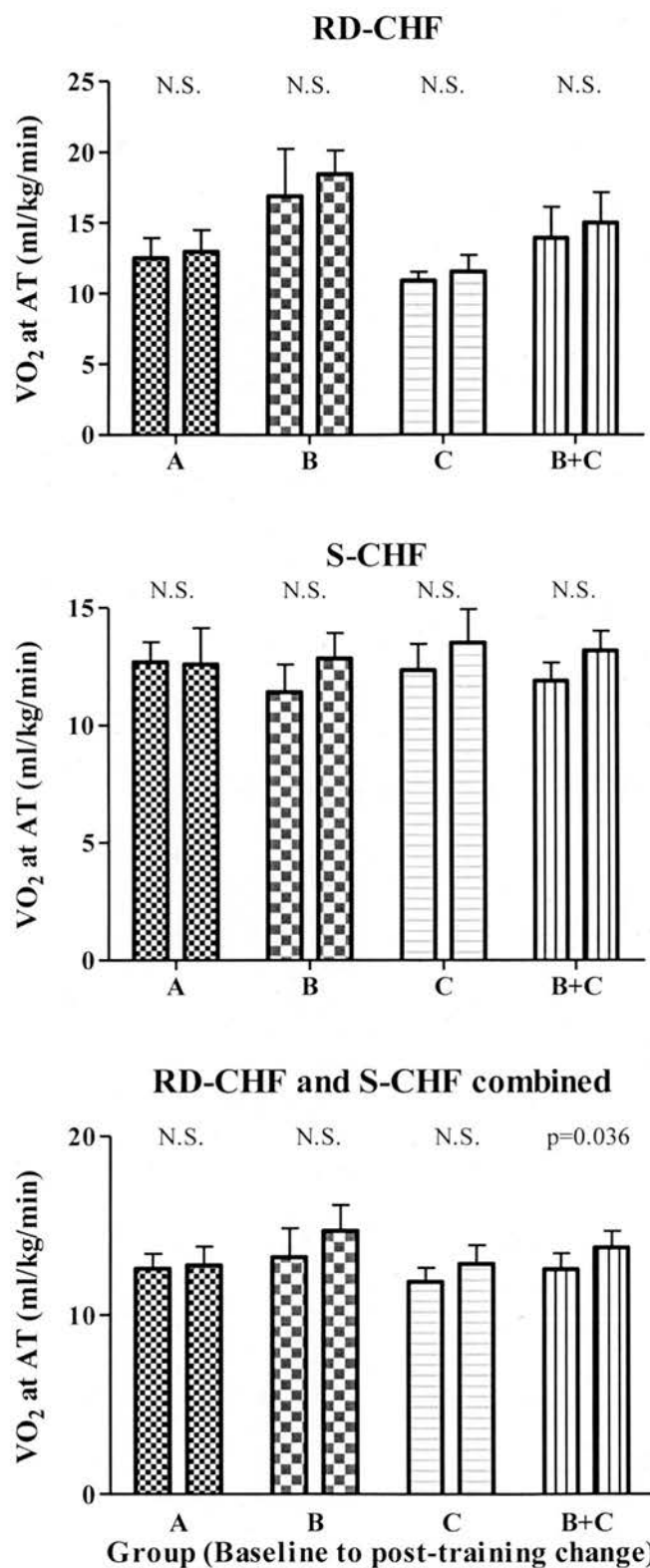


Figure 7.2. VO_2 at anaerobic threshold at baseline and after training for control and exercising groups. A, control group; B, bike group; C, NMS group, B+C, all exercising. RD-CHF, recently decompensated patients; S-CHF, stable patients only. N.S., not significant.

	Group	Baseline	After training	<i>p</i>
NYHA	A	2.14 ± 0.363	2.14 ± 0.363	-
	B	2.0 ± 0	1.5 ± 0.548	0.076
	C	2.22 ± 0.441	2.11 ± 0.333	0.347
	B+C	2.13 ± 0.352	1.87 ± 0.516	0.041
6MW (m)	A	505 ± 135	526 ± 135	0.053
	B	617 ± 35.4	646 ± 66.0	0.077
	C	510 ± 155	517 ± 154	0.381
	B+C	553 ± 131	569 ± 139	0.046
Treadmill time (s)	A	546 ± 181	581 ± 188	0.194
	B	647 ± 170	722 ± 198	0.055
	C	563 ± 235	655 ± 187	0.030
	B+C	599 ± 207	683 ± 188	0.002
Quadriceps strength (kg)	A	33.6 ± 11.1	34.4 ± 9.33	0.58
	B	42.8 ± 9.70	47.8 ± 10.8	0.067
	C	28.6 ± 12.9	33.4 ± 16.7	0.027
	B+C	34.2 ± 13.5	39.2 ± 16.0	0.002
Fatigue index	A	0.62 ± 0.182	0.60 ± 0.121	0.607
	B	0.70 ± 0.184	0.68 ± 0.158	0.825
	C	0.79 ± 0.205	0.8 ± 0.085	0.917
	B+C	0.75 ± 0.196	0.75 ± 0.130	0.943
NT-pro BNP (pg/ml)	A	926 ± 1227	649 ± 1165	0.3
	B	1623 ± 1383	1113 ± 961	0.173
	C	1802 ± 2071	1274 ± 1461	0.021
	B+C	1721 ± 1752	1209 ± 1248	0.005

Table 7.2. Pre and post training performance and NT-pro BNP data for combined recently decompensated and stable patients. A, Control group, n=14; B, Bike group, n=7; C, NMS group, n=10; B+C, all exercising, n=17.

7.4.3 Exercise training vs. controls

When the exercise training groups were combined, significant improvements in NYHA functional class, 6MW distance, treadmill exercise time, quadriceps strength, NT-pro BNP, VO₂ at AT and OUES were observed following the training period (Table 7.2 and Table 7.3). Interestingly, a significant deterioration in OUES and VE/VCO₂ slope was

observed in group A (controls) for the same period; the remaining assessment parameters were unchanged in this group.

7.4.4 Effects of detraining

Change in assessment parameters over the entire course of the study, including the detraining period, were also examined (Figure 7.3). No significant differences were observed in parameters measured immediately post-training and following the detraining period. The most noticeable changes were observed in the bike group for treadmill exercise time, peak VO_2 , VO_2 at AT and NYHA functional class. Although these

		Baseline	After training	<i>p</i>
p VO_2 (ml/kg/min)	A	18.6 ± 3.65	18.7 ± 4.67	0.78
	B	20.5 ± 6.75	22.8 ± 8.62	0.109
	C	18.7 ± 4.47	18.8 ± 3.69	0.93
	B+C	19.6 ± 5.54	20.8 ± 6.66	0.15
VO_2 at AT (ml/kg/min)	A	12.6 ± 2.75	12.8 ± 3.43	0.78
	B	13.2 ± 3.97	14.7 ± 3.53	0.159
	C	11.9 ± 1.90	12.9 ± 2.57	0.15
	B+C	12.6 ± 3.05	13.8 ± 3.10	0.036
VE/ VCO_2	A	26.2 ± 4.83	31.0 ± 8.65	0.034
	B	27.3 ± 6.27	28.2 ± 8.09	0.633
	C	30.1 ± 3.80	24.6 ± 3.89	0.043
	B+C	28.7 ± 5.15	26.4 ± 6.34	0.161
OUES	A	2.33 ± 0.699	1.78 ± 0.437	0.023
	B	1.93 ± 0.596	2.04 ± 0.604	0.307
	C	1.78 ± 0.840	2.17 ± 0.560	0.067
	B+C	1.86 ± 0.699	2.11 ± 0.560	0.032

Table 7.3. Pre and post training cardiopulmonary data for combined recently decompensated and stable patients. A, Control group, n=14; B, Bike group, n=7; C, NMS group, n=10; B+C, all exercising, n=17.

measures were not statistically significant between visit dates for the bike group with the exception of NYHA class, there is a trend for more sustained improvement in the bike group compared with NMS and controls. Only NYHA class was significantly improved in the bike group after detraining as compared with controls (control 2.1 ± 0.316 , bike 1.6 ± 0.548 , $p=0.041$).

7.5 Discussion

Previous studies of exercise training in chronic heart failure have focussed on patients with stable symptoms (Belardinelli *et al.*, 1999; Dubach *et al.*, 1997a; Hambrecht *et al.*, 1995; Wielenga *et al.*, 1999). To our knowledge, no study has yet investigated the effect of exercise training in patients with recently decompensated symptoms. There is evidence that the RD-CHF patients in this study were more unwell than S-CHF and control patients: NT-pro BNP levels were higher at baseline, blood pressure was lower and there was a higher drop-out rate from the study in the RD-CHF group. Despite this finding, significant improvement in NT-pro BNP was observed in the RD-CHF group following training. The majority of this effect was due to changes observed in the NMS group. Further work is required to clarify whether this reflects a genuine improvement in heart failure as a beneficial effect of NMS or whether this is a statistical anomaly since NT-pro BNP also fell to a lesser degree in RD-CHF control patients. Up-titration of ACEi and beta-blocker therapy occurred in few RD-CHF patients during the exercise training period but equally between control, bike and NMS subjects, and in no patients from the S-CHF group. However it is difficult to altogether exclude the possibility that improvement observed following training with NMS in NT-pro BNP was not due to the

increases in medical therapy concomitant with the training regime.

It is not clear whether training in RD-CHF patients is safe owing to the small number of participants in this study. However, no adverse events were noted in the RD-CHF group, either with training or during performance assessment, although one patient was readmitted to hospital with worsening CHF. Additionally, 44% of the RD-CHF group dropped out of the study, 6 prior to randomisation, and, as such, were excluded from the final analysis. Further studies involving larger numbers of RD-CHF patients would be required to clarify the tolerability of exercise training in recently decompensated patients.

Patient motivation was poorer following a recent admission with decompensated symptoms. Their decreased functional status was reflected in the number of subjects who were recruited to the study initially but who were unable to complete baseline exercise assessments and were subsequently excluded – 5 in this group compared with 1 in the stable group. 3 further patients dropped out of the study prior to the post training period assessment, all from the recently decompensated group. 2 of these patients were using conventional bike training, 1 NMS and none from the control group. This indicates that in a more severely affected patient population, exercise training is much more difficult to provide in a sustained way. Overall, 32% of the recently decompensated group as a whole and 37.5% of the recently decompensated group randomised to exercise therapy were unable to complete the exercise training period. However, the overall numbers of patients randomised were too small to draw any firm conclusions at this stage as to which exercise regime was best tolerated.

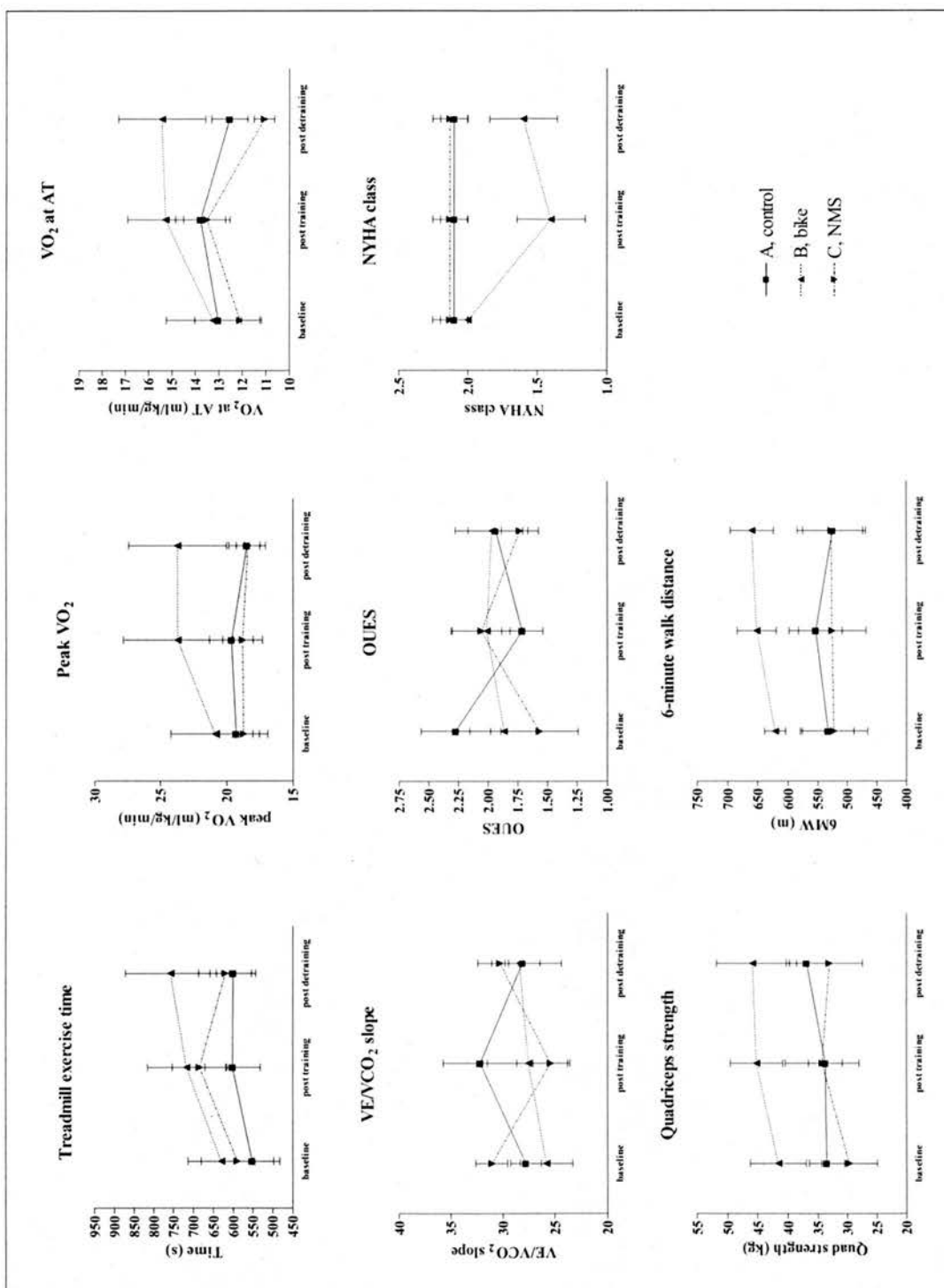


Figure 7.3. Assessments post training and post washout periods.

NMS has previously been shown to improve exercise performance including cardiopulmonary parameters, muscle strength and fatigability (Dobsak *et al.*, 2006) and to induce beneficial changes in muscle fibre composition and oxidative capacity (Nuhr *et al.*, 2003; Theriault *et al.*, 1994), pro-inflammatory state and endothelial function (Karavidas *et al.*, 2006). In this study we demonstrated improvements in 6MW distance, quadriceps strength, treadmill exercise time, NT-pro BNP, OUES and VO_2 at AT when data from the NMS and bicycle groups were combined. A trend for improvement in 6MW distance was observed for the bike group, and OUES for the NMS group when exercise regimes were examined separately. The lack of statistical significance seen may have been due to the low number of patients who completed the exercise training period. Improvements remained significant for the NMS group in treadmill exercise time, quad strength, NT-pro BNP and VE/VCO_2 slope when exercise regimes were examined separately. It is interesting that VE/VCO_2 slope significantly deteriorated in the control group, was apparently unaltered in the bike group and significantly improved in the NMS group. Whilst these data do not prove that NMS is any better or worse than conventional training, they do indicate that NMS is superior to no exercise therapy and is worthy of further investigation.

Data obtained following a 6-week period of detraining is limited by the small number of patients completing this part of the study. There is a trend for sustained improvement in peak VO_2 and VO_2 at AT seen in the bike group, and treadmill exercise time in the NMS group. However, none of the data from assessment after detraining reached statistical significance compared with controls. This is likely to be due to the small numbers of

subjects in each group completing this section of the study and so no firm conclusions about this can be made. One recent study has examined the role of detraining in the CHF patient (Tenenbaum *et al.*, 2006). In this study, patients exercised for either 1.6 years or 3 years and were reassessed at 3 years. Results suggest that continued exercise therapy is required to maintain the benefits that result from conventional training. No data yet exists for detraining following NMS but it is likely that continued therapy will be required, or NMS used as a bridging therapy until conventional training can be performed.

Training regimes used in heart failure exercise trials usually involve aerobic exercise which requires an increase in cardiac work. Although we have not encountered adverse events during conventional training programmes or during cardiopulmonary exercise testing, exercise-induced arrhythmia is a theoretical concern and may limit the acceptability of exercise rehabilitation to prescribing clinicians. Additionally, the target population that may benefit from exercise training are generally less well motivated and have more comorbidities than trial populations previously studied. As such, we designed this study to include patients who had recently been admitted to hospital with an acute decompensation of their heart failure. Exercise rehabilitation in this setting would more closely mirror, in timing of introduction, rehabilitation that is offered following acute myocardial infarction. Neuromuscular stimulation is an alternative to conventional aerobic or resistance training. Although the degree of patient motivation required to use NMS due to discomfort and adjustments necessary should not be underestimated, it is easier to perform than conventional exercise and may be more suitable to use in the

deconditioned and demotivated heart failure population.

7.6 Conclusions

Improvements in symptoms and functional capacity are observed when RD-CHF patients are included in an exercise training programme, a group previously excluded from studies. However, these patients have a higher drop-out rate from exercise programmes compared with stable CHF patients. Neuromuscular stimulation appears to be effective in patients with recently decompensated heart failure and may be a useful mode of delivery of exercise where conventional training is not practicable.

8 Study 5. Participants suitable for inclusion in exercise training trials are substantially different from the general heart failure population.

8.1 Abstract

8.1.1 Introduction.

Exercise training in stable chronic heart failure (CHF) is safe and beneficial. However, patients included in previous studies appear to be highly selected in terms of age, comorbidities and motivation. This study compares characteristics of patients able to undertake a clinical trial of exercise training with the population of CHF patients they were recruited from. Similar data has not been previously reported in the literature.

8.1.2 Methods.

672 patients were screened in a tertiary centre, either following acute admission or following outpatient attendance. Patients included in the register had documented left ventricular systolic dysfunction and clinical evidence of CHF not attributable to an alternative cause. Standard exercise trial inclusion and exclusion criteria were applied to assess suitability to participate. Patients were subdivided into those with a recent hospital admission due to decompensated CHF within the previous month (RD-CHF) and stable CHF (S-CHF). The data from the ExTraMATCH meta-analysis were used as a comparison group.

8.1.3 Results.

Only 45 (6.70%) of the screened patients were eligible to participate based on age, ability to exercise and perform functional status tests required for the exercise training study. 34 patients (5.06%) were subsequently randomised. 23 patients (3.42%) completed the entire study protocol. 68.3% of eligible patients were taking at least weekly exercise prior to recruitment compared to 18.0% of non-eligible patients ($p<0.001$). Eligible patients were younger, had similar NYHA class, had fewer comorbidities and were more likely to be treated with ACEi, B-blockers, aldosterone antagonists and digoxin ($p<0.05$ in all cases) compared with non-eligible patients. After inclusion, a trend for earlier dropout from the study was observed for RD-CHF ($p=0.077$). In addition, O_2 uptake efficiency was lower ($p=0.027$) and VE/VCO_2 slope ($p=0.002$) and NT-pro BNP ($p=0.014$) were higher in patients who dropped out from the study.

8.1.4 Discussion.

Recruitment of CHF patients representative of the population seen in the clinical setting to participate in exercise training studies is difficult and standard exclusion criteria select younger, fitter patients, commonly already participating in regular exercise. Trial patients were younger and were on more specific CHF therapies. RD-CHF patients more closely represent the wider CHF population but drop-out rate from the exercise training study was high. Alternative trial designs are needed to investigate the role of training in the general CHF population who may have much to gain from this therapy.

8.2 Introduction

Exercise training in chronic heart failure (CHF) has been demonstrated to be safe and to produce beneficial effects for exercise performance, neurohormonal imbalance, inflammation and quality of life (Adamopoulos *et al.*, 2002; Belardinelli *et al.*, 1999; Coats *et al.*, 1992; Tyni-Lenne *et al.*, 2001). There may also be a mortality benefit (Piepoli *et al.*, 2004). Guidelines relating to exercise training limit recommendation to stable CHF patients (Swedberg *et al.*, 2005) and no randomised controlled study has to our knowledge explored exercise training in the recently-decompensated heart failure group. As such, no data for this subset of CHF patients exist. There is a concern that the characteristics of CHF patients previously included in trials do not accurately reflect the wider CHF population. This limits the applicability of exercise training programmes and may be one reason why some guidelines do not recommend exercise training programmes as strongly as others (Hunt *et al.*, 2005; Scottish Intercollegiate Guidelines Network, 1999). In most studies, males are over-represented, patients are younger than the peak incident age of heart failure and have fewer co-morbid conditions. Additionally, study patients need to be highly motivated in order to participate in exercise programmes of up to 3 years in duration and this may not be representative of the general heart failure population who tend to be demotivated, detrained and often depressed (Faris *et al.*, 2002; Jiang *et al.*, 2007). Medical management of trial patients is usually stabilised and optimal, again not reflecting real-world practice in all cases.

This issue highlights an additional limitation of published trial evidence relating to exercise training. Most trials have included patients that have been stable for at least 3

months prior to randomisation. There are no published randomised controlled studies, to our knowledge, that have attempted to explore exercise training in recently decompensated heart failure patients and, as such, no safety or efficacy data for this subset of patients exist.

In attempting to explore these issues further, we screened CHF patients in a tertiary centre and explored the relationship between eligible patients able and willing to participate in a training study with the non-eligible heart failure population. The differing characteristics and ability to complete a simple exercise training study of stable heart failure patients (S-CHF) and patients recently admitted to hospital with decompensated symptoms (RD-CHF) were also examined. This is important since if exercise training programmes are to be introduced more widely in clinical practice, the applicability of training to the wider population of CHF patients needs to be examined critically.

8.3 Methods

8.3.1 Registry data

Patients were screened in a tertiary centre teaching hospital, either following acute admission or following attendance at an outpatient clinic as discussed in section 3.1.2. Consent for details to be included in the registry was obtained verbally from each patient. Case notes were reviewed and the patient was interviewed and, where necessary, examined by either a heart failure specialist nurse or a cardiologist. Patients were included in the register only if they had symptoms and signs consistent with heart

failure, including breathlessness and/or evidence of salt/water retention not attributable to an alternative cause. Data were entered into a multi-relational database (Microsoft Access 2000) as described in section 3.5. Information in the register was updated with each new attendance e.g. readmission, clinic visit, home visit or attendance at a specialised beta-blocker up-titration clinic. The screening period was from October 2001 until December 2003.

8.3.2 Study inclusion

Patients from the registry were screened for their suitability for inclusion in an exercise training research study. Inclusion and exclusion criteria for participating in the exercise training programme are discussed in section 3.1. Inclusion criteria included age between 18 and 80 years, symptomatic heart failure NYHA grade II or above and documented left ventricular systolic dysfunction graded at least moderate on previous echocardiography or LV angiography. Exclusion criteria included any current active participation in an exercise programme, a history of stroke or acute coronary syndrome within the 3 months prior to recruitment, uncontrolled anginal symptoms and any respiratory, neurological or orthopaedic condition which would prevent their participation in either a conventional bicycle exercise training programme or the physical performance assessments during the study. Two categories of patient were recruited – recently decompensated heart failure patients (RD-CHF, section 3.1.2) and stable heart failure patients (S-CHF, section 3.1.1). RD-CHF patients were recruited following a hospital admission with worsening symptoms of heart failure and worsening and uncontrolled peripheral oedema or pulmonary oedema defined clinically and on

chest radiograph. Following agreement to participate in the study, they were seen between 2 and 4 weeks following discharge and baseline performance assessments were made. S-CHF patients were recruited from the outpatient setting and were defined as having had no admission with heart failure, no change in their symptom status and no adjustment of their heart failure medication over the 3 months prior to recruitment.

8.3.3 Comparison group

The ExTraMATCH pooled data is used as a comparison group. The studies from which the dataset was identified were selected according to the criteria in Table 8.1. The criteria are similar to the inclusion and exclusion criteria used for the S-CHF study patients. Individualised patient data are not available from the ExTraMATCH publication and, as such, it is not possible to merge the published data split between training and control group patients presented in the paper. There were no differences at baseline between the two groups and, as such, the trained patients' data are used for comparison (n=395).

8.3.4 Study protocol

Study subjects underwent assessment on four occasions. Two initial assessments were

Randomised parallel group controlled trials
Evaluation of exercise training only with no other intervention studied simultaneously
Stable heart failure only (3 months or more)
Left ventricular systolic impairment with ejection fraction less than 50%
At least 8 weeks of exercise training
Training regimes targeting at least both legs
Survival data available of at least 3 months duration

Table 8.1. Inclusion criteria for ExTraMATCH meta-analysis datasets.

performed at least 24 hours apart prior to randomisation with data from the first assessment discarded and the second assessment data used as baseline. Patients were randomised to one of three groups as described in section 3.4.1. Group A acted as controls and undertook usual activity with no specific exercise training regime. Group B exercised 5 days per week for 30 minutes per day using a recumbent bicycle. Group C exercised for 30 minutes per day, five days per week using neuromuscular stimulation of the quadriceps and gastrocnemius muscles. A third assessment was performed within 5 days of the end of a 6-week training period. A final assessment was then made after a further 6-week period of “detraining” during which patients were neither encouraged nor discouraged from taking part in any form of physical training. At each visit subjects performed a 6-minute walk test (section 3.3.2), a symptom-limited cardiopulmonary treadmill exercise test (section 3.3.4) and an isometric quadriceps strength and fatigue test (section 3.3.3). Cardiopulmonary exercise data were collected during a symptom-limited modified Bruce treadmill exercise test and patients were encouraged to exercise to the point of exhaustion beyond their anaerobic threshold. Anaerobic threshold (AT) was determined by the V-slope method (section 3.3.4.3). Oxygen uptake efficiency slope (OUES) was calculated as described in section 3.3.4.5. VE/VCO_2 slope was calculated as described in section 3.3.4.4. Blood was collected for N-terminal pro-BNP analysis at baseline assessment and within 5 days of completing the exercise training programme as described in section 3.3.7.

8.3.5 Data analysis

Data were analysed as described in section 3.6 with *SPSS for Windows* version 13.0 and

a p value of <0.05 was considered statistically significant. Data are presented as mean \pm standard deviation unless otherwise stated. Nominal data were analysed using the Pearson Chi-square test with Fisher's exact test where appropriate. Scale data were analysed using independent t-test or one-way ANOVA with post-hoc Bonferroni test for normally distributed data and the Mann-Whitney U test for non-parametric data. Survival analysis was performed using the Kaplan-Meier method with subsequent log-rank analysis of survival curves.

8.4 Results

8.4.1 Population characteristics

672 patients were screened over a 26-month period between October 2001 and December 2003. Table 8.2 shows baseline characteristics of the screened group. 115 (17.1%) patients died during the screening period. Of the screened patients, only 413 (61.5%) were eligible for inclusion on age criteria. Applying the additional exclusion criteria as detailed in the methods section above, 45 (6.70%) were eligible for inclusion

	Mean	
Age (years)	74.7 \pm 11.6	Range 31.1 – 102.6
Duration of heart failure since diagnosis (years)	2.48 \pm 2.48	Range 0 – 27.1
Sex M:F	377 : 295	56.1 : 43.9 (%)

Table 8.2. Screened population characteristics.

and were contacted for further assessment. Of these patients, 5 did not perform baseline tests due to worsening of heart failure symptoms resulting in readmission. A further 6 attended for baseline assessment but were excluded from the study before being randomised due to an inability to complete baseline performance assessments due to physical limitation from either heart failure symptoms or angina. 34 patients (5.06%) were randomised. 5 patients dropped out of the study during the exercise phase (4 RD-CHF) patients, 3 from group B (Bike) and 2 from group C (NMS). 29 patients (4.31%) therefore completed the exercise training programme. A further 6 dropped out before the final assessment could be undertaken, 3 S-CHF and 3 RD-CHF, leaving a final sample of 23 patients from the original 672, representing 3.42% of the originally screened population.

Table 8.3 shows the characteristics of patients originally considered eligible for inclusion in the study compared with the non-eligible patients. Eligible and non-eligible

		Mean	p
Age	Non-eligible	74.5 ± 11.5	<0.001
	Eligible	64.8 ± 10.7	
Sex M:F (%)	Non-eligible	344 : 283 (54.9 : 45.1)	0.011
	Eligible	33 : 12 (73.3 : 26.7)	
Aetiology, n (%)*	Non-eligible	352 : 217 (61.9 : 38.1)	0.104
	Eligible	23 : 22 (51.1 : 48.9)	

Table 8.3. Differing characteristics of study population vs. patients not suitable for study based on inclusion and exclusion criteria.*Ischaemic vs. non-ischaemic patients.

patients had similarly severe symptoms of heart failure – 56.0% of non-eligible patients were in NYHA functional class 3 compared with 44.4% of eligible patients ($p=0.093$). 72.8% of non-eligible patients had LV systolic dysfunction graded as moderate or severe compared with 91.1% of eligible patients ($p=0.003$). 18.0% of non-eligible patients volunteered that they took at least weekly exercise prior to inclusion in the registry compared with 68.3% of eligible patients ($p<0.001$).

Differences between non-eligible, RD-CHF, S-CHF and ExTraMATCH patients are shown in Table 8.4. RD-CHF, S-CHF and ExTraMATCH patients were significantly younger than the non-eligible population ($p<0.001$ in all cases). Age of RD-CHF and S-CHF patients was not significantly different ($p=0.193$). ExTraMATCH patients were significantly younger than the RD-CHF group ($p=0.001$). NYHA class was similar for all four groups with no statistically significant differences observed between them. Mean duration of heart failure since initial diagnosis was significantly longer for S-CHF patients compared with non-eligible patients ($p<0.001$) and there was a trend for longer duration of heart failure since diagnosis in S-CHF patients compared with RD-CHF patients ($p=0.054$). RD-CHF patients did not have a statistically longer duration of CHF

	Non-eligible	RD-CHF	S-CHF	ExTraMATCH
Age (years)	74.5 ± 11.5	66.2 ± 11.9	61.9 ± 7.00	60.5 ± 9.30
NYHA status	2.60 ± 0.59	2.48 ± 0.51	2.33 ± 0.49	2.60 ± 0.60
Duration of CHF since diagnosis	2.38 ± 3.38	3.03 ± 3.66	4.45 ± 3.39	N/A

Table 8.4. Differences between non-eligible, RD-CHF, S-CHF and ExTraMATCH patients.

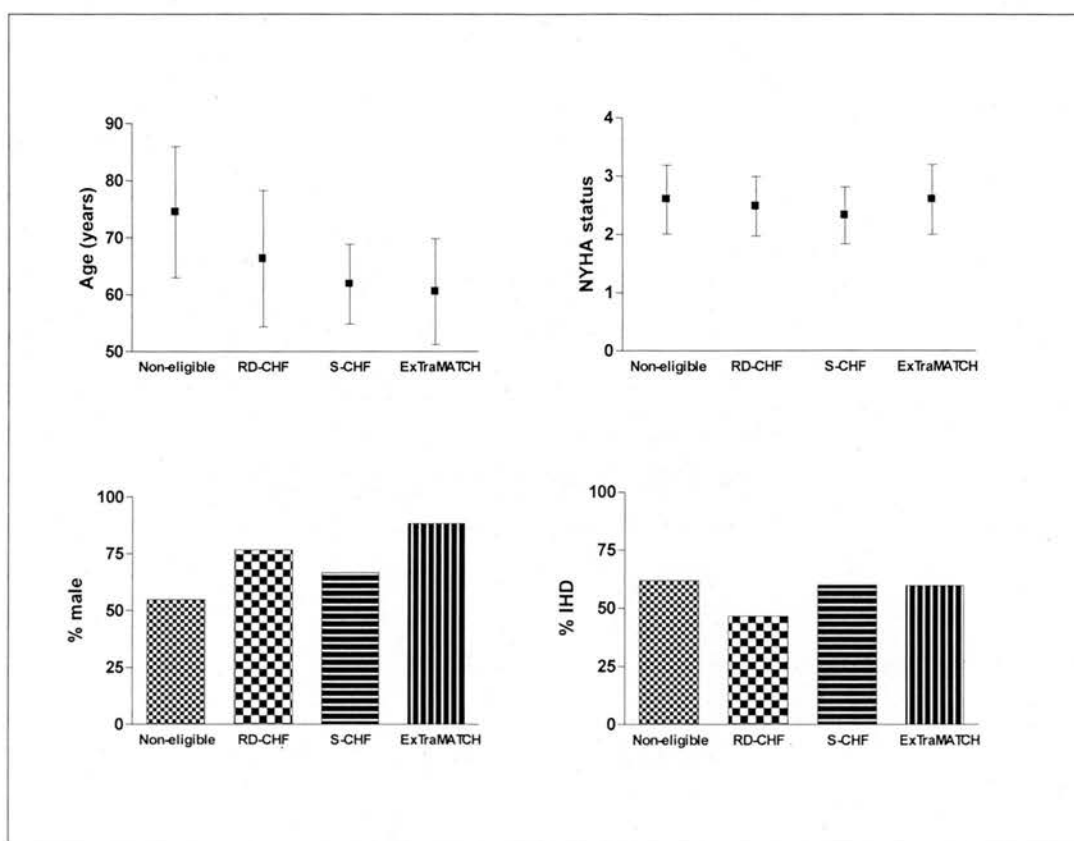


Figure 8.1. Age, NYHA class, proportion of male and ischaemic patients for non-eligible, S-CHF, RD-CHF and ExTraMATCH patients.

compared with non-eligible patients ($p=0.149$). No data from ExTraMATCH regarding duration of CHF since diagnosis were available.

Age, NYHA class and percentage of male patients and those with an ischaemic aetiology for their CHF are shown in Figure 8.1. The sex ratio was similar between non-eligible patients and S-CHF patients ($p=0.262$). Males were over-represented in the RD-CHF group compared with non-eligible patients ($p=0.014$) and in the ExTraMATCH group compared with non-eligible patients ($p<0.001$). There was a trend for over-

representation of non-ischaemic patients in the RD-CHF group compared with non-eligible patients ($p=0.072$) but S-CHF and ExTraMatch had similar ratios on non-ischaemic to ischaemic patients as the non-eligible population ($p=0.54$ and $p=0.28$, respectively).

8.4.2 Comorbid conditions

Comorbid conditions were recorded in the database for 661 patients. A total of 207 different diagnoses were logged in the register (see Appendix C). The mean number of additional comorbid conditions between non-eligible, RD-CHF and S-CHF patients was not significantly different: for non-eligible heart failure patients the mean number of comorbidities was 4.93 ± 2.64 , for RD-CHF patients was 5.53 ± 2.65 and for S-CHF patients was 5.71 ± 3.02 . However, differences between the three populations were observed when comorbidities were grouped into the following categories: valvular heart disease, atrial arrhythmias, ventricular arrhythmias, significant respiratory disease, peripheral vascular disease, renal impairment, diabetes, cerebrovascular disease and carcinoma. Mean comorbidities when grouped in this way were 1.64 ± 1.28 for non-eligible patients, 1.67 ± 1.03 for RD-CHF patients and 1.07 ± 0.88 for S-CHF patients; RD-CHF and non-eligible patients were not significantly different ($p=0.884$), the smaller number of comorbid conditions approached significance between RD-CHF and S-CHF ($p=0.051$) and was significantly different between non-eligible and S-CHF patients ($p=0.027$). No single comorbid condition was significantly more prevalent between the three populations when individual conditions were examined separately (data not shown). No data on co-morbid conditions for the ExTraMATCH group were available.

8.4.3 Hospital admissions

The number of admissions during the screening period was examined. For the entire registry the mean number of admissions was 1.21 ± 0.57 , range 1-5. Mean number of admissions of non-eligible patients was 1.18 ± 0.55 , for RD-CHF patients was 1.63 ± 0.76 and for S-CHF was 1.27 ± 0.46 . The number of admissions in the RD-CHF group was significantly more than the non-eligible population ($p=0.003$) and approached significance for the increased number of admissions compared with the S-CHF group ($p=0.052$). Non-eligible and S-CHF patients were not significantly different ($p=0.503$).

8.4.4 Medications

Total number of prescriptions for each patient entered into the registry was examined along with prescriptions for individual classes of drug. Mean number of medications was 4.89 ± 1.87 , range 1-10. Interestingly male patients were on significantly more medications than female patients (5.18 ± 1.91 and 4.52 ± 1.76 , respectively, $p<0.001$). CHF patients with an ischaemic aetiology were on more medications than those with a non-ischaemic aetiology (5.41 ± 1.82 and 4.17 ± 1.69 , respectively, $p<0.001$). Total number of prescribed medications differed between non-eligible and eligible patients. Non-eligible patients were on fewer medications than RD-CHF patients (mean 4.82 ± 1.87 and 5.73 ± 1.66 , respectively, $p=0.006$) and S-CHF patients (5.93 ± 1.77 , $p=0.037$). RD-CHF and S-CHF were not on significantly different numbers of medications ($p=0.732$).

Table 8.5 shows prescription of individual classes of medication between non-eligible, RD-CHF, S-CHF and ExTraMATCH training group patients; these data are represented in Figure 8.2. In the ExTraMATCH group, antiplatelet usage was significantly lower compared with non-eligible patients ($p<0.001$) and with RD-CHF patients ($p=0.009$), but no differences were observed between non-eligible and RD-CHF or S-CHF patients. ExTraMATCH patients were more likely to be using warfarin than any other group

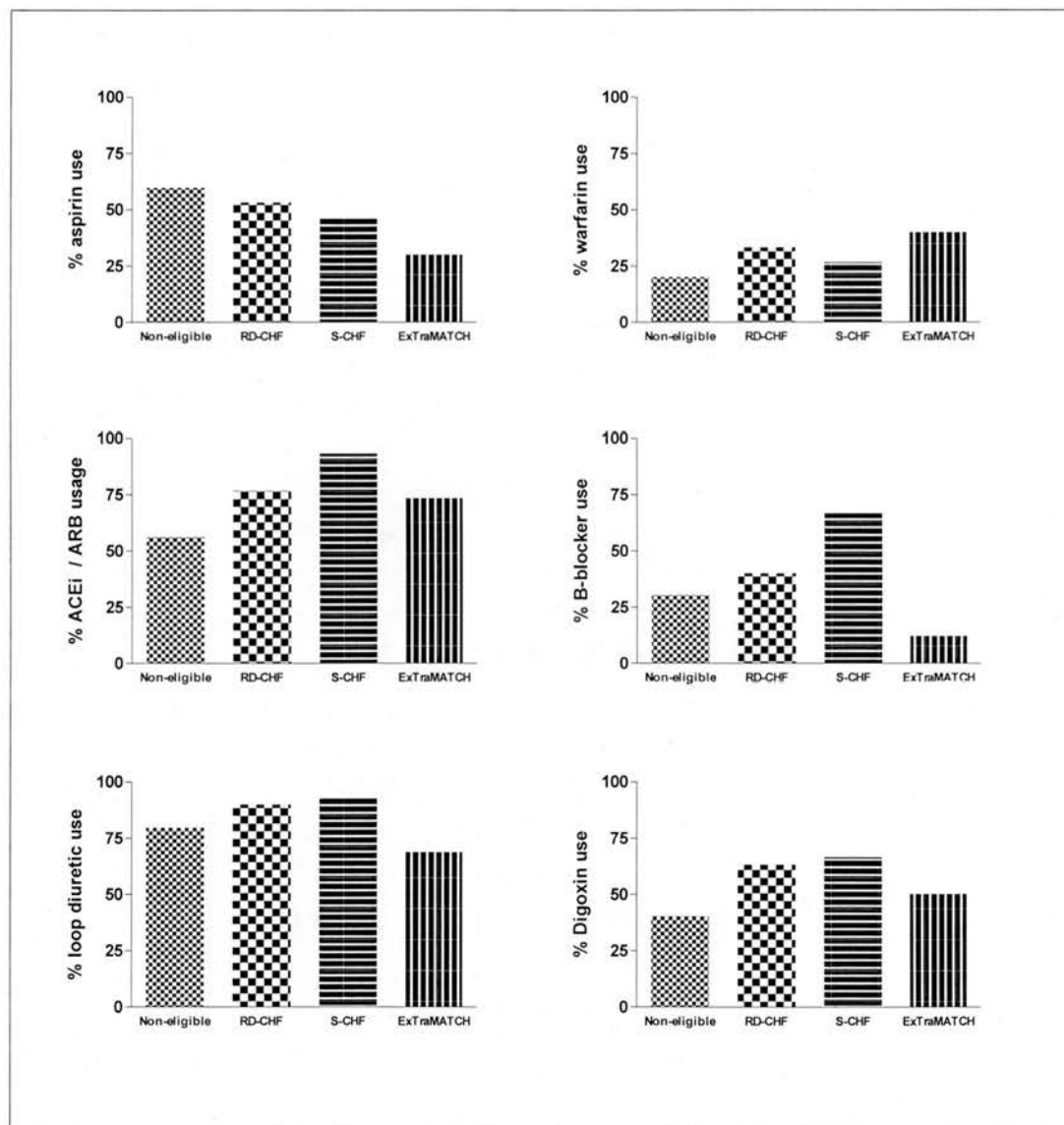


Figure 8.2. Medication prescription between non-eligible, RD-CHF, S-CHF and ExTraMATCH patient groups. Combined cardioselective and non-cardioselective B-blocker use is shown.

($p<0.001$). RD-CHF, S-CHF and ExTraMATCH patients were more likely to be on ACEi / ARB therapy compared with the non-eligible group ($p=0.019$, $p=0.002$ and $p<0.001$, respectively). RD-CHF, S-CHF and ExTraMATCH patients did not differ amongst themselves for ACEi/ARB usage. S-CHF patients were more likely to be on a heart-failure specific beta-blocker than non-eligible patients ($p=0.004$) and all beta-blocker usage in the ExTraMATCH group was significantly lower than all 3 other groups ($p<0.001$ in all cases). No difference in loop diuretic use was seen between non-eligible, RD-CHF and S-CHF patients. Loop diuretic use was significantly lower in the ExTraMATCH patients compared with non-eligible, RD-CHF and S-CHF patients ($p<0.001$ in all cases). Digoxin was used more for RD-CHF, S-CHF and ExTraMATCH patients compared with non-eligible patients ($p=0.011$, $p=0.038$, $p=0.001$, respectively).

Medication class	Non-eligible (n=627)	RD-CHF (n=30)	S-CHF (n=15)	ExTraMATCH
Anti-platelet	375 (59.8)	16 (53.3)	7 (46.7)	119 (30.1)
Warfarin	126 (20.1)	10 (33.3)	4 (26.7)	158 (40)
ACEi/ARB	352 (56.1)	23 (76.7)	14 (93.3)	290 (73.4)
Non-CS B-Blocker	35 (5.82)	1 (3.33)	1 (6.67)	
CS B-blocker	155 (24.7)	11 (36.7)	9 (60.0)	48 (12.2)
Loop diuretic	500 (79.7)	27 (90.0)	14 (93.3)	272 (68.9)
Thiazide diuretic	46 (7.33)	4 (13.3)	2 (13.3)	
Aldosterone antagonist	151 (24.1)	15 (50.0)	5 (33.3)	
Digoxin	253 (40.4)	19 (63.3)	10 (66.7)	199 (50.4)
Statin	187 (29.8)	15 (50.0)	10 (66.7)	

Table 8.5. Pearson Chi-square test for number of prescriptions of individual classes of medications. Total n = 672. Data expressed as n (%). CS – cardioselective.

No data from ExTraMATCH were available for thiazide, aldosterone antagonist or statin use. No difference in thiazide usage was seen between non-eligible, RD-CHF and S-CHF groups. RD-CHF patients were more likely than non-eligible patients to be using aldosterone antagonists ($p=0.002$) but there was no difference between non-eligible and S-CHF patients. Statin usage was higher in RD-CHF patients and S-CHF patients compared to non-eligible patients ($p=0.019$ and $p=0.004$, respectively).

8.4.5 Dropout from study

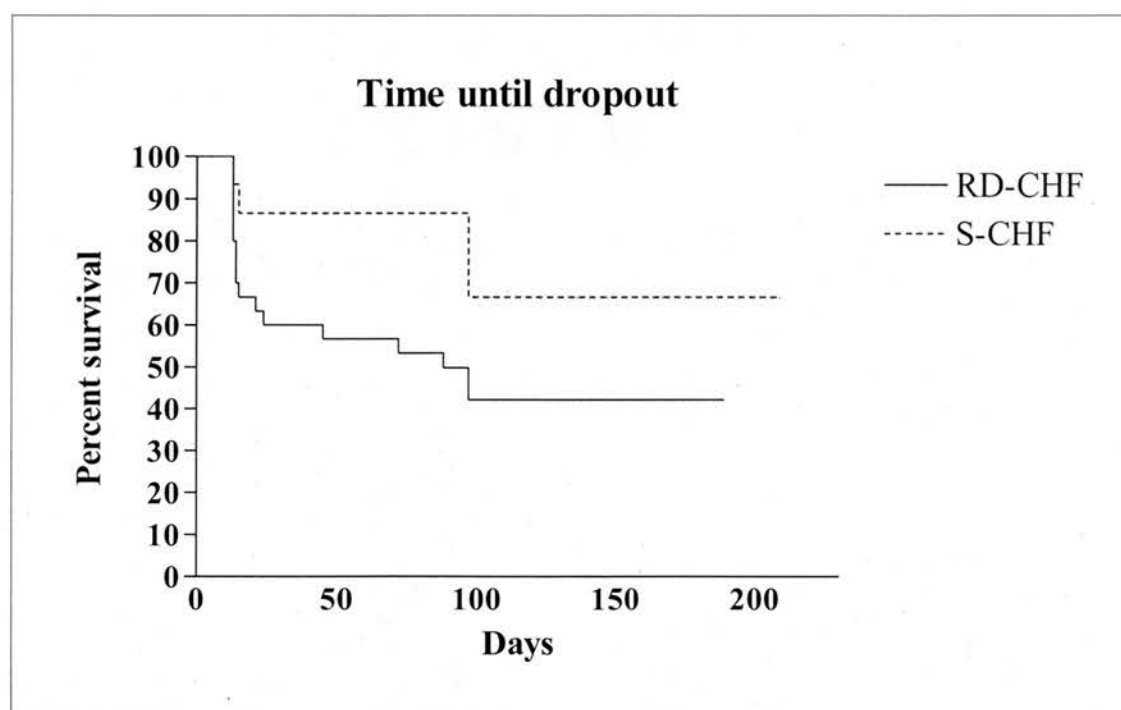


Figure 8.3. Kaplan-Meier survival curve for RD-CHF and S-CHF study patients – time until dropout from study.

Figure 8.3 shows the Kaplan-Meier survival curve for dropout from the exercise training study for RD-CHF and S-CHF groups. Although there is a trend for earlier dropout in the RD-CHF group, this difference did not reach statistical significance (log-rank $p=0.077$).

40 patients undertook performance testing and serum collection for NT-pro BNP analysis. Differences were observed for physical performance between patients who were and were not able to complete the study (Figure 8.4). Differences between dropout groups by one-way ANOVA were not significant for treadmill exercise time ($p=0.776$), peak VO_2 ($p=0.172$), VO_2 at anaerobic threshold ($p=0.533$), 6MW ($p=0.158$), maximal leg strength ($p=0.521$) and fatigue index ($p=0.304$). Significant differences by one-way

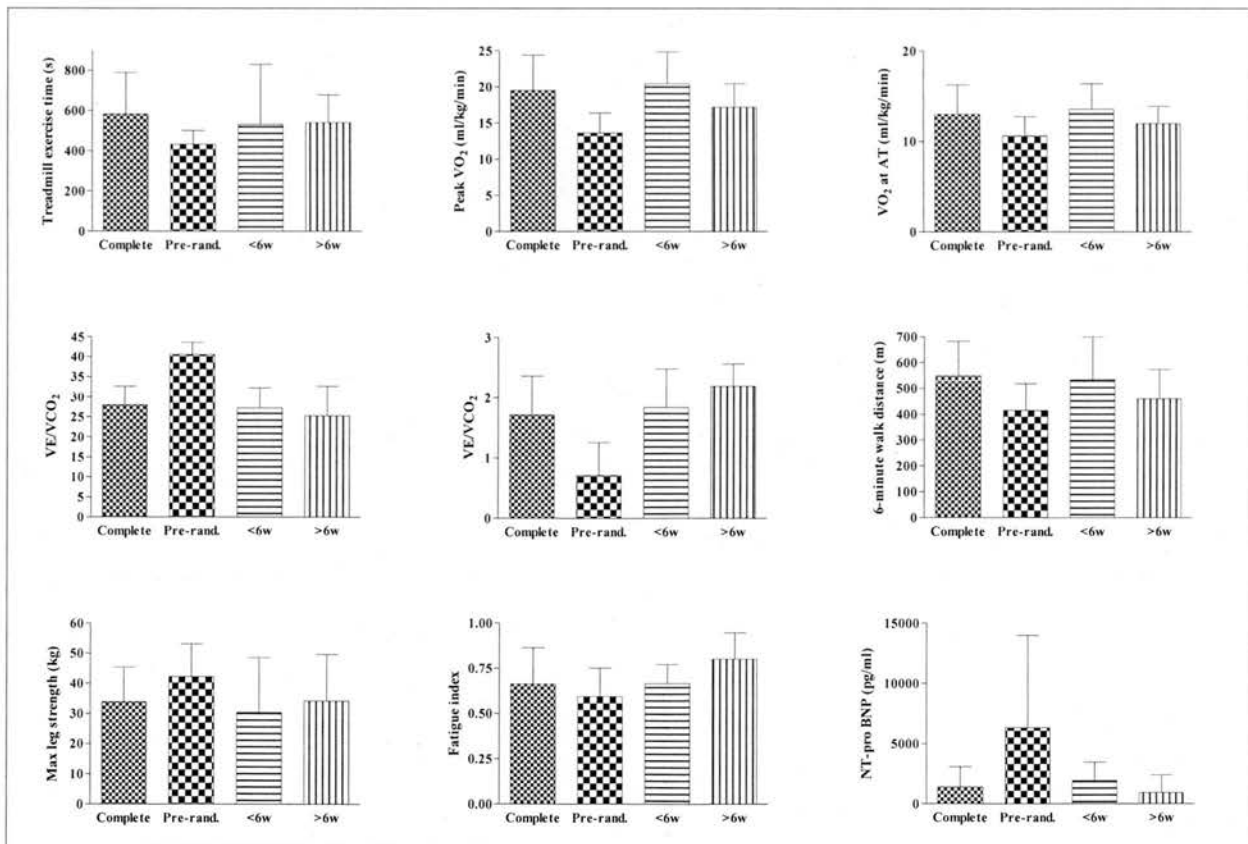


Figure 8.4. One-way ANOVA comparison of performance between patients completing study and patients dropping out pre-randomisation (pre-rand.), prior to end of training period (<6w) and prior to end of detraining period (>6w).

ANOVA were observed for VE/VCO₂ slope ($p=0.002$), OUES ($p=0.027$) and NT-pro BNP ($p=0.014$). VE/VCO₂ slope for patients who dropped out prior to randomisation was significantly higher than those patients who completed the study (40.5 ± 3.08 and 28.0 ± 4.56 , respectively, $p=0.002$), those who dropped out before the end of the training period (27.2 ± 4.96 , $p=0.009$) and those who dropped out prior to the end of the detraining period (25.2 ± 7.34 , $p=0.009$). OUES for patients who dropped out prior to randomisation was significantly lower than those patients who completed the training period but dropped out prior to the detraining period (0.714 ± 0.542 and 2.19 ± 0.370 , respectively, $p=0.023$) and a trend for lower OUES between those dropping out prior to randomisation and those completing the study was observed (0.714 ± 0.542 and 1.72 ± 0.640 , respectively, $p=0.080$). NT-pro BNP was higher in patients who dropped out prior to randomisation compared with patients who completed the entire study (6302 ± 7651 pg/ml and 1401 ± 1664 pg/ml, respectively) and patients who completed the exercise training period but who dropped out prior to the end of the detraining period (926 ± 1445 pg/ml). Non-parametric post-hoc tests did not reach significance, however.

Figure 8.5 shows the survival curve for the 34 patients who were subsequently randomised to training or control groups. No difference in time to dropout from study was observed between training groups and controls (log-rank $p=0.589$).

8.5 Discussion

Current guidelines recommend exercise training as part of the treatment of stable chronic heart failure (Hunt *et al.*, 2005; Swedberg *et al.*, 2005). Previous studies have

used differing training regimes and as such no single training modality is recognised to be superior to another (Rees *et al.*, 2004). Rehabilitation services similar to those offered to survivors of acute myocardial infarction are not routinely in place for heart failure patients outside of clinical trials and this may be due to the differing characteristics of trial and general CHF populations.

Despite a substantial burden of heart failure both in the community and resulting from hospitalisation (Alla *et al.*, 2007; Rodeheffer, 2003; Thomas and Rich, 2007), few patients screened were suitable for this exercise training trial based on standard inclusion and exclusion criteria. Of the 6.7% suitable, only 4.3% completed the exercise training

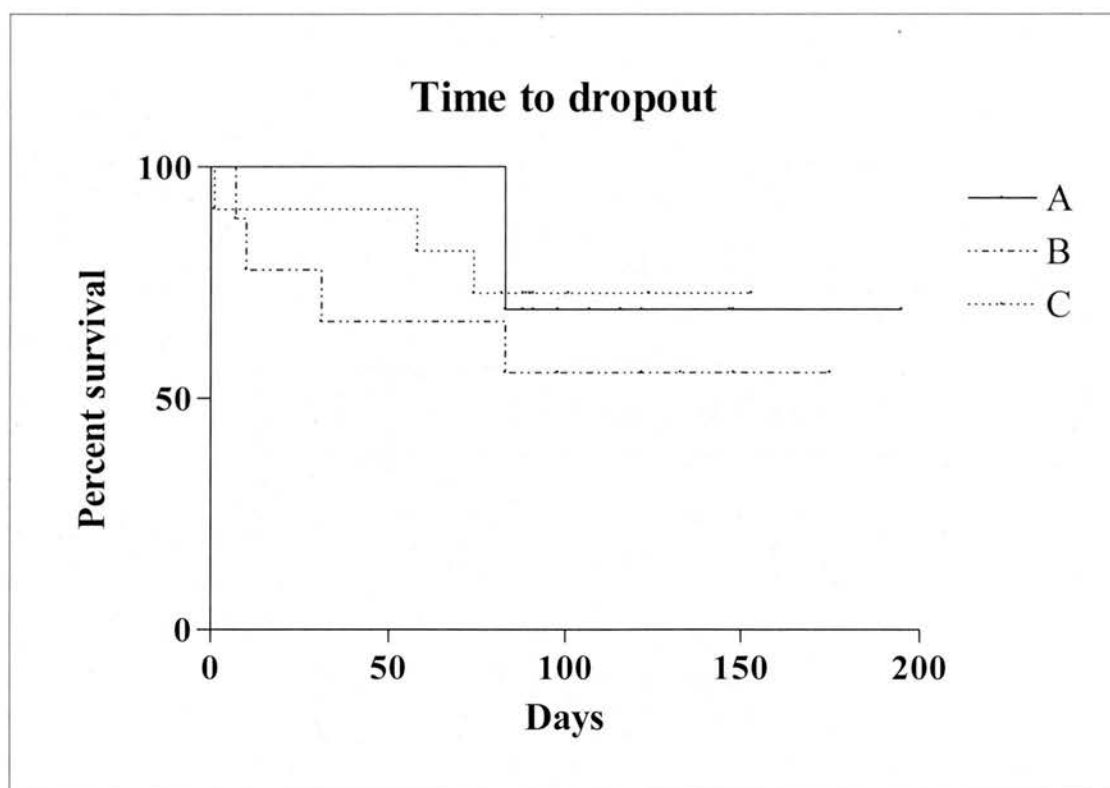


Figure 8.5. Kaplan-Meier survival curve for randomised study patients – time until dropout from study. n=34. A, control group; B, bike group; C, NMS group.

section and only 3.42% were still participating at the end of the study.

Although symptoms of heart failure were similar between eligible and non-eligible groups, eligible patients were younger, more likely to have a non-ischaemic aetiology and had a higher degree of LV systolic impairment. RD-CHF patients more closely mirrored the screened population with S-CHF patients having less severe symptoms, younger age and a longer duration of heart failure since original diagnosis compared with RD-CHF patients.

RD-CHF and S-CHF study patients were more likely to be on ACEi or ARB, cardioselective beta-blockers, aldosterone antagonists or digoxin compared with non-eligible patients. Interestingly, although CHF patients with an ischaemic aetiology were not over-represented in the study population compared to the non-study population, study patients were more likely to be on a statin. In contrast, despite a high proportion of ischaemic patients in the ExTraMATCH training group, there was relatively little aspirin use. There was a relatively low usage of beta-blocking agents in ExTraMATCH (no detail is given to indicate whether the agents used were cardioselective or non-cardioselective), and the high usage of warfarin and digoxin in the ExTraMATCH group suggests a high proportion of patients with atrial fibrillation. Alternatively, the lower usage of beta-blockers and higher usage of digoxin may reflect the era in which the trials comprising the pooled ExTraMATCH data were undertaken. No details regarding thiazide diuretic, aldosterone antagonist or statin use are given in the ExTraMATCH publication. p-values given in Table 8.5 refer to within group comparisons of non-eligible, RD-CHF and S-CHF patients only.

S-CHF patients were more likely to be on ACE inhibitor / angiotensin II receptor blocker therapy, cardioselective beta-blockers and aldosterone antagonists than RD-CHF or non-study patients. Interestingly, statin use was higher in the S-CHF group despite a higher proportion of patients with a non-ischaemic aetiology of CHF.

Comorbid conditions were similar between RD-CHF and non-study populations. S-CHF patients had significantly fewer comorbid conditions than non-study patients when comorbidities were grouped. S-CHF and RD-CHF patients were also on more medications than non-study patients.

Overall, S-CHF patients typical of those normally recruited for heart failure exercise training studies were fitter, younger and were on better pharmacological therapy for heart failure than the much larger group of non-study patients. Although RD-CHF patients were more closely related to non-study patients, their recruitment into a training study was difficult and there was a trend for earlier dropout from the study in this group. Dropout was associated with more severe ventilatory inefficiency (higher VE/VCO₂ slope, lower OUES) and raised NT-pro BNP levels, all surrogate markers of heart failure severity. A larger sample size in future may allow prediction of which patient is likely to be able to complete or maintain a training programme. For now, although training is an attractive adjunct in the treatment of CHF, the applicability of trial results to the general CHF population is uncertain in view of the differing characteristics between the two groups. Most CHF patients previously included in trials of exercise training are likely to be highly selected and the applicability of this evidence to the wider CHF population is questionable. Until further data exist for the older, less fit CHF patient, training will

continue to be recommended for the younger, fitter and better motivated CHF patient only.

9 Discussion

9.1 NMS as a training modality

Study 1 was designed as a pilot experiment to explore the concept of NMS and assess its safety. In these respects, this study was successful. Improvement in functional capacity was observed for both training groups. Findings are consistent with those of other investigators who have observed improvement in functional performance following this form of training although these have been small trials of between 14 and 30 patients with no control group included in the designs (Deley *et al.*, 2005; Dobsak *et al.*, 2006; Maillefert *et al.*, 1998). With this uncontrolled trial design, it is impossible to be certain that improvement is due to the intervention itself as improvement may have been observed as part of the natural course of these patients illness. As such, firm conclusions regarding the efficacy of NMS and the interchangeability with conventional training regimes cannot be drawn pending controlled studies. Care was taken to ensure that the change in performance seen between baseline and post-training in study 1 was not due to increased familiarity with the assessments themselves, however. One study investigating the effects of NMS in a transplant population was controlled and showed improvement in peak VO_2 following NMS training for 8 weeks with baseline peak VO_2 slightly lower at around 17 ml/kg/min compared with those observed in study 1 of around 19 ml/kg/min (Vaquero *et al.*, 1998). Knee extensor muscle strength has been shown to increase following NMS in both an uncontrolled and a controlled study design (Quittan *et al.*, 2001; Quittan *et al.*, 1999a) and improvements have been observed in muscle mass although beneficial changes in oxidative capacity are less obvious (Maillefert *et*

al., 1998) compared with those seen following conventional training (Adamopoulos *et al.*, 1993). The findings in study 1 suggest that NMS is effective as a training modality as is conventional training, although the degree of benefit will probably differ between the two modalities and that the systemic and local effects may be different. Certainly, NMS has been identified as a useful form of rehabilitation / training in other populations such as spinal cord injury (Hillegass and Dudley, 1999) although the conditions relating to impaired performance in this patient population and the CHF population differ (i.e. denervation and disuse atrophy compared with maladaptive fibre type distribution, disuse, cachexia). The protocol used for stimulation varies markedly between studies also. Previous investigators have suggested that low frequency (25Hz) NMS, such as that used in study 1, reduces fatigability and results in improvement in muscle strength in human and animal subjects (Badylak *et al.*, 1990; Maillefert *et al.*, 1998) although higher frequency protocols (50Hz) have also been used (Quittan *et al.*, 2001; Quittan *et al.*, 1999a). Stimulation frequency has been explored more fully in animal models. Low frequency stimulation protocols using frequencies of between 10 and 20 Hz have been shown to result in increased fatigue resistance at the expense of decreased muscle strength and oxidative capacity (Donselaar *et al.*, 1987; Eerbeek *et al.*, 1984; Kernell *et al.*, 1987b; Kernell *et al.*, 1987a). Little information is available regarding higher frequency regimes in humans, although in a cat model, intermittent use of a high frequency stimulation period during low-frequency training largely prevented the loss of strength seen with low frequency regimes alone (Kernell *et al.*, 1987b). The use of an alternating high frequency / low frequency protocol in study 4 was used to specifically avoid the theoretical problems which may be associated with purely low-frequency

protocols.

There is evidence to suggest that a combination of NMS with resistance loading is more effective in generating improvement in human muscle fatigue resistance and strength (Bajd *et al.*, 1989; Peckham *et al.*, 1976) and further studies to assess the role of conventional training facilitated by NMS are required.

No improvement in peak VO_2 was seen in study 1 following NMS training or indeed conventional training, despite improvement in 6MW, treadmill exercise time and muscle strength and fatigue. This may have been due to methodological problems with the assessment of peak VO_2 using the original Morgan Benchmark equipment, or due to problems with compliance with the training regimes, or with the training regimes themselves. It is not possible to assess the contribution of each of these potential problems. Compliance could not be reliably checked in study 1, other than by verbal report from the study patients. This may be unreliable, of course, as patients may have been eager to be helpful with the study and unwittingly give the impression that they have exercised, either with NMS or the bike, more than is actually the case. This issue was partially addressed in study 4 with the post-training check of the bike odometers. NMS diaries and verbal reports from patients using NMS remain the only assessment of compliance with NMS usage in a home environment, however, which is unsatisfactory. Similarly, the adjustment of stimulator output (amplitude) during the course of a training session is vital as adaptation occurs over the 30-minute period with visibly less contraction occurring after every 5-10 minutes. Increasing the output can be potentially uncomfortable for the subject which introduces a conflict – in a demotivated patient

group whom we think are unlikely to tolerate conventional training programmes, the tolerability and acceptability to the patient of a training programme which introduces some discomfort to the patient cannot be underestimated.

I suspect that for NMS to be truly effective in improving muscle strength, fatigue resistance and oxidative capacity, some form of resistance element needs to be introduced. This could take the form of conventional bike exercise coupled with low frequency NMS although a more comfortable and secure method of affixing the electrodes would be required, e.g. a modified pair of shorts with electrodes pre-positioned. Alternatively, resistance training using a modified quadriceps bench could be used. Finally, although not strictly-speaking resistance training, a more practical alternative would be to use extended periods of NMS combined with walking. Using this method combined with secure electrode placement may allow extended periods of NMS use and would allow a better trial using sham NMS vs. true NMS. Unfortunately, extended periods of NMS may be less comfortable as the electrode interface gel dries out. Furthermore, precise positioning of the electrodes to encourage maximal fibre recruitment could be problematic.

9.2 Safety of NMS

One final aim of study 1 was to assess the safety of NMS. I did not encounter any adverse events with NMS use and this is consistent with the findings of other investigators. I could find no report in the literature regarding injury relating to NMS and no adverse cardiovascular effects were observed when NMS was performed in hospital on a small series of 5 patients. Equally, pulse and blood pressure were checked

for every patient being instructed in the use of NMS prior to the start of their exercise period in studies 1-4. No changes were observed. Case reports have suggested possible inappropriate discharge of implantable defibrillators due to electromagnetic interference during NMS therapy (Wayar *et al.*, 2003) but other preliminary data exist suggesting that NMS protocols utilising electrode positions distant from implantable devices do not cause sufficient interference to induce pacemaker or ICD malfunction, an issue which will become increasingly relevant over the next decade as more patients undergo device therapy for CHF (Crevenna *et al.*, 2004; Crevenna *et al.*, 2003). Overall, I conclude that NMS is safe for patients without implantable devices, but the safety for those with devices remains uncertain and further study is required in this area.

9.3 Body composition

Study 2 examined whether NMS and conventional exercise training regimes were associated with alterations in body composition assessed by DEXA scanning. Although changes in functional capacity were seen, including an improvement in peak VO_2 for conventional exercise and a trend in peak VO_2 for NMS exercise when corrected for skeletal muscle mass, no change in body composition was observed. The hypothesis that NMS would result in increased muscle mass following training was rejected. The changes in muscle mass and oxidative capacity following conventional training are well documented already (Nuhr *et al.*, 2004; Quittan *et al.*, 2001), but few data exist regarding changes in muscle composition following NMS in a heart failure population. The improvement in peak VO_2 following this form of training may be due to increased muscle mass, beneficial fibre type shift or improved oxidative capacity, and it is unclear

what the relative contribution of each is. Unsurprisingly, in study 2, a strong correlation between peak VO_2 and lean muscle mass was observed. Little improvement was seen in peak VO_2 following training, with peak VO_2 increasing only in the bike training group and only when corrected for skeletal muscle mass. This is likely to be due to a number of factors, including the greater level of physical fitness seen in the predominantly NYHA II group, reflected by higher baseline peak VO_2 s, limiting the potential gains and the larger muscle groups exercised with the bike training regime compared with NMS. Compliance may have been better with conventional exercise – there was no reliable way to check compliance in studies 1-3. No change in muscle mass was observed following training and this may have been due to a number of factors, including underpowering of the study to detect a change using DEXA scanning, potentially ineffective training, or qualitative changes in muscle function rather than quantitative changes in muscle mass. Improvement was seen in treadmill exercise time, 6MW and leg strength / fatigue, and as such, I think that training was effective to an extent. It may be that longer NMS training regimes result in quantitative changes in muscle mass and this could be the focus for further research. As yet, no similar data exist in the literature using DEXA scanning following NMS training, and little data after any form of training in CHF, so it is difficult to put the findings of this study in the context of others' work.

9.4 Inflammatory indices

There is no doubt that a pro-inflammatory state exists in heart failure with the degree of inflammatory response closely associated with disease severity and progression, as discussed in section 6.2. It is not yet absolutely certain whether inflammation is

causative or reflective of disease severity / progression. For instance, mast cell density and propensity for degranulation and release of vasoactive and pro-inflammatory mediators from mast cells is elevated in human cardiomyopathy (Patella *et al.*, 1998). The pro-inflammatory mediators released may be responsible for endomyocardial fibrosis seen in heart failure and there is evidence in a mouse model that mast cell deficient animals do not develop myocardial dilatation decompensated heart failure in response to pressure overload following aortic banding (Hara *et al.*, 2002). TNF α is negatively inotropic and induces cardiomyopathy (Bryant *et al.*, 1998; Finkel *et al.*, 1992; Hara *et al.*, 2002; Hegewisch *et al.*, 1990). As such, the pro-inflammatory state may be causative in the progression of heart failure and limiting / reversing this state may have functional and prognostic benefits. The hypothesis of study 3 was that the pro-inflammatory state observed in CHF could be attenuated by neuromuscular electrical stimulation. This effect was not observed following NMS training, however. As discussed in section 6.5, a reduction in TNF α and IL-6 was not seen following either method of training in this study in contrast to other studies which have utilised conventional exercise training methods (Adamopoulos *et al.*, 2002; Larsen *et al.*, 2001). sTNF α fell in the bike training group but not the NMS group. The discrepancy between this and other studies includes underpowering of the study although Adamopoulos, *et al.* (2002) exercised only 24 heart failure patients. These patients were less well, however, with slightly lower peak VO $_2$ s at baseline and lower ejection fractions but the most likely explanation for the difference in findings for conventional exercise is the shorter exercise training duration in our study. With only 6 weeks of training, potential gains in functional performance and fall in levels of circulating cytokines may not have had time

to develop. Again, compliance may have been a contributing factor and the smaller muscle mass exercised with NMS will have influenced the results when compared to conventional training. Additionally, sTNF_{r2} is probably less vulnerable to acute changes in inflammatory state induced by exercise or intercurrent illness for reasons already discussed in section 6.5 and this may explain the change seen on the bike group only. With a small group of study patients, sampling blood in a quiet, relaxed environment may not be sufficient to remove the 'noise' seen with measurement of cytokines sensitive to acute changes in clinical state, such as TNF α .

Overall, the hypothesis that NMS attenuates the pro-inflammatory response in heart failure was rejected. However, a larger trial could be designed to investigate this further as it is unclear whether the lack of change seen was simply due to under-powering as there was some evidence of change following conventional training. If sufficient patients could be recruited to a larger trial, it would be interesting to measure pro-inflammatory cytokines throughout the training period allowing any trends for change with training to emerge. This type of trial would have to include an appropriate control population of similarly sick CHF patients, perhaps in a crossover design. Although it is unclear whether the pro-inflammatory state is directly causative in the pathogenesis of CHF or simply a surrogate marker of disease activity, measurement of cytokines and other markers appears to be a marker of efficacy following an intervention in heart failure and on this basis, NMS as used in this study was less effective than conventional exercise; this may have important prognostic implications.

9.5 NMS and decompensated heart failure

Study 4 was designed to investigate the hypothesis that patients with recently decompensated symptoms would show an increment in peak VO_2 and other markers of severity / functional capacity including NT-pro BNP following NMS training. The safety and tolerability was compared to conventional training and also overall with NMS and conventional training in stable CHF patients. A control group of RD-CHF and S-CHF patients was also included for comparison. Recruitment for this study was challenging for reasons which were explored further in chapter 8. Following randomisation, 32% of the RD-CHF group as a whole and 37.5% of RD-CHF patients randomised to undertake some form of exercise training discontinued the study prematurely. This high dropout rate significantly limits the interpretation of the study, but some inferences can be made. RD-CHF patients had more severe CHF symptoms and higher levels of circulating NT-pro BNP, as expected, but there was attenuation of NT-pro BNP following NMS exercise in the RD-CHF group above that seen in the control group, and this finding was repeated when S-CHF patients were included, with no reduction in NT-pro BNP being seen in the bike training group when RD-CHF and S-CHF patients were analysed separately or together. Treadmill exercise time improved for NMS training as did quadriceps strength when RD-CHF and S-CHF patients were analysed together. This is in keeping with the findings from study 1 and also implies that selected RD-CHF patients do have something to gain from training. No previous study has explored the effects of exercise in the recently decompensated patient group and as such this study forms the basis for future research. Early rehabilitation is offered to survivors of myocardial infarction and I believe that appropriate exercise training could

be offered safely to survivors of decompensated heart failure. A major barrier to this however is the patient's functional status and motivation. Although I believe that NMS is better tolerated and easier to perform than bike exercise, a degree of motivation is required to perform it properly and consistently. A better way of applying the electrodes is required to maximise muscle recruitment and to reduce patient discomfort. At present, quite small electrodes have been used which deliver current to a relatively small area over the skin (approximately 4cm^2). This requires quite accurate placement of electrodes over quadriceps and gastrocnemius to ensure maximal recruitment with minimal discomfort. I know from my experience that such optimal electrode position varied between patients and that movement from one position to another tended to degrade the electrode gel, resulting in more patient discomfort during stimulation. Compliance would be poorer if the patient experienced more discomfort than was necessary and was required to increase the stimulator output more frequently to observe an effect. Therefore, a better system to use larger electrodes and would have better skin contact. For a subsequent study, I think a better system would use an elastic material containing large electrodes, such as lycra shorts, with a liberal application of conductive liquid/gel applied before the shorts are put on. For the purposes of patient comfort, I do not think gastrocnemius stimulation should be used in a further trial as the muscle mass recruited in comparison to quadriceps is small and it would be important to limit the complexity of the intervention in order to make it more acceptable to the patient.

A further trial of NMS in the recently decompensated patient would be worthwhile on the basis of the results from study 4. The benefits of conventional training in patients

with stable symptoms is well established but delivery of conventional training to RD-CHF patients is difficult and the benefits are not obvious from study 4. The next trial should look at NMS in isolation in order to simplify the design. Exclusion criteria in study 4 primarily relate to the ability to perform some of the functional assessments and to perform bicycle exercise training. A simplified study of NMS vs. control patients with recently decompensated symptoms would be less prone to patient drop-out if simple functional assessments were made, such as 6MW, quality of life score, leg strength and fatigue and cycle ergometer VO_2 assessment. My experience has been that patients find cycle ergometer cardiopulmonary exercise tests easier to perform, accepting that there are some methodological differences in the interpretation of the results. Patients with minor orthopaedic or neurological disease, or simply severe heart failure who would have been unable to perform a symptom-limited treadmill cardiopulmonary exercise test would not necessarily be excluded by such a trial design.

9.6 Influence of training duration

A longer duration of exercise training, e.g. 20 weeks, should also be used. One of the reasons that studies 1 and 4 show less beneficial change for markers of functional capacity than other investigators have found is likely to be the short period of exercise – 15 hours in total over a six-week period. The Cochrane review of 29 randomised controlled trials of exercise training in CHF infers that longer therapy durations results in greater improvement in functional capacity (Rees *et al.*, 2004). A longer exercise period would allow more exploration of the tolerability and safety of NMS and would allow the effect of alteration of medication to be diminished. Large numbers of patients

with CHF experience a decompensation of their symptoms and require intervention by a heart failure nurse in the community or hospital admission. At the time of discharge, adjustments are made to medical therapy and a criticism of study 4 is that adjustments of ACEi and diuretic dose did occur in the immediate post-discharge period for RD-CHF patients, although these alterations occurred equally between NMS, bike and control groups. It cannot be said with certainty, however, that the beneficial effects of NMS seen could not have been compounded by changes in medical therapy. In a large metanalysis of exercise training in CHF, only six out of the nine studies examined were able to provide information regarding changes in medical therapy during the study period representing approximately two thirds of the patients studied (Piepoli *et al.*, 2004). It was stated that there were no alterations in ACEi, B-blocker or aldosterone antagonist prescription / dosage during the trial period but that patients were permitted to alter the dosage of their loop diuretic therapy as required. No information was available from the other three studies and it is impossible to altogether exclude an effect of medical therapy on outcome during these trials.

A criticism of a longer exercise period for recently decompensated patients of course is that after a few weeks if they continue to participate in the study, they are effectively stable. As such, the only truly unstable patients are the ones who drop out of the study. This concept makes statistical analysis to determine the benefits of NMS in recently decompensated patients very difficult and so there is an argument for simply trialling NMS in stable patients first over a long period to demonstrate efficacy, and trialling NMS over a short period in recently decompensated patients to demonstrate safety.

Some patients are discharged with a degree of peripheral oedema remaining. My experience (with patients not included in any of the above studies) has been that NMS in the presence of oedema results in current shunting and discomfort with no meaningful muscle recruitment. As such, a delay of only two weeks following hospital discharge may not be sufficient to allow time for removal of all oedema in the current climate of early nurse-supported hospital discharge. This may be a factor in future trial design and also in the clinical utilisation of NMS – if a small number of patients report adverse experiences with NMS due to discomfort secondary to such shunting, clinicians will be unlikely to recommend it routinely to many patients.

9.7 Recruitment challenges

Recruitment for clinical trials is recognised to be difficult (Lovato *et al.*, 1997), particularly amongst the older population (Ory *et al.*, 2002) and in those patients who live at a greater distance from the trial centre (Lovato *et al.*, 1997; Petrovitch *et al.*, 1991). There is no reason for CHF to be an exception. Although the National Service Framework recommends rehabilitation for patients with CHF (Department of Health, 2000), it is recognised that this is a service infrequently available in the UK and uptake may be poor. Uptake of rehabilitation following myocardial infarction is lower in the elderly, in female and in ethnic minority groups (Evenson *et al.*, 1998; Evenson and Fleury, 2000; McGee and Horgan, 1992; Parks *et al.*, 2000) and as discussed in section 2.2, females and elderly patients are over-represented in the general CHF population. Limited data exist regarding the difficulties in CHF exercise training trial recruitment, unfortunately. Only two published papers investigate this issue. In the first, a

randomised American trial of behavioural therapy in CHF (Chang *et al.*, 2004), similar exclusion and inclusion criteria to those in study 5 were used – patients were in NHYA functional class II-III, ejection fraction was <40% indicating at least moderate impairment of LV systolic function, and they were not participating in an exercise / rehabilitation programme prior to enrolment. Patients were screened from an outpatient database and patients with ejection fractions <40% on the basis of results from either cardiac catheterisation, radionuclide scanning or echocardiography were flagged. Patients were invited to participate by letter and subsequently by telephone. They were required to attend the study centre once per week for 90 minutes for 15 weeks if randomised to the education arm; in addition they were to use relaxation tapes lasting 15-20 minutes twice per day if randomised to the relaxation arm. Those randomised to usual care were not required to attend the study centre. Those required to attend were reimbursed for travel expenses and all patients were given a total of \$100 if they completed the entire study period. This contrasts with the patients in study 5 who were screened following hospital admission and who were offered no financial incentives to participate in the study. The recruitment period was 2 years, 3 months, similar to that in study 5. Of the 1920 patients screened in this study, only 29% were eligible, with high or unknown EF cited as the reason for exclusion. This is very similar to the number excluded during our screening process – from 672 patients, 192 (28.6%) were excluded in view of no, mild or an unknown degree of LV systolic dysfunction. Of the eligible patients, 65 out of 551 did not turn up for assessment and a further 315 declined to participate. Of the 126 consenting to participate, 36 were ineligible because their heart failure symptoms were either too mild or too severe, or they were already participating

in a similar rehabilitation or relaxation programme. A further 46 either did not complete the screening or did not turn up for the baseline assessment. Ultimately only 18% (85) of the 482 eligible patients were enrolled. Transportation problems and lack of willingness to participate in the study accounted for 56% of those people who declined to continue following screening. Little additional information regarding the characteristics of non-eligible patients are presented in this study with most of the data pertaining to those who were eligible but declined. Of those who declined, symptoms and medications were similar to those who participated, but those who declined were older.

The second published study is a trial of relatively low-intensity exercise training in a CHF population. This trial is currently underway but the difficulties encountered in patient recruitment have recently been published (Jolly *et al.*, 2007). This is a trial designed to assess the benefits of low intensity exercise in a group of CHF patients in addition to their enrolment in a heart failure nurse liaison programme. The outcomes of this trial are yet to be reported. Patients have been recruited after referral to the heart failure nurse liaison service and considered eligible based on the following inclusion criteria – at least moderate LV systolic impairment as judged visually or based on a measured EF of <40%, previous NYHA functional class II-III symptoms or an admission due to decompensated CHF within the previous two years and stable symptoms over the previous four weeks. Patients were excluded if they had NYHA class IV symptoms, were unable to speak English, were hypotensive, had significant angina or structural heart disease, had had a recent stroke or MI or recent involvement with a rehabilitation programme, had any psychiatric or dementing illness, had significant

respiratory compromise or any mechanical reason for not being able to exercise. As such, inclusion and exclusion criteria were very similar to the S-CHF patients recruited in study 5. Of the 1639 patients screened, only 39% were eligible based on the above criteria. In fact 468 patients did not have sufficiently severe heart failure symptoms, significantly impaired EF or a recent admission with decompensation. This is different from our screening process as all patients had either been admitted or had had a previous symptomatic episode. Of the remaining 529 non-eligible patients, 204 had non-cardiac comorbidities and 153 had cardiac reasons for exclusion. 54 (10%) were excluded due to problems with remote residence and transport issues which contrasts with the higher percentage of drop-out due to this reason cited in the relaxation therapy study above (Chang *et al.*, 2004). Of the remaining 642, 289 declined to participate or failed to attend for assessment and 184 were excluded following more detailed clinical assessment.

It will be interesting to see the baseline characteristics of patients recruited to this study when it is published and compare the participants with the original eligible group. 169 (10%) patients were eventually randomised following a 19-month screening process in this study, a similar duration to ours, but targeting patients who were stable – over half of our recruitment was directed at patients with a recent decompensation. There is no doubt that recruitment of RD-CHF patients was more difficult and this is reflected in the lower proportion of the original screened group who eventually participated. No information is recorded, unfortunately, regarding the reasons cited by patients in our study for not wishing to be involved in the study. However, it is clear from the above 2 studies and from study 5 presented here that it is difficult to recruit these patients into

clinical trials of exercise training. Additionally, the population of CHF patients recruited into studies of exercise training, whether they are stable or recently decompensated patients, are significantly different from the screened population from which they are drawn. The RD-CHF patients do seem to more closely resemble the general heart failure population in terms of age and severity, but recruiting this group and maintaining their involvement within an exercise training study is particularly challenging.

Low rates of patient recruitment over the course of the study resulted in statistical underpowering of study 4 and has limited the interpretation of the findings. To further assess the benefits of early rehabilitation for RD-CHF patients a longer recruitment period would be required. Measuring the benefits of training over a short period as was performed in study 4 is, I think, still valid as a longer period of training would blur the distinction between recently decompensated and stable patients. However, a much larger trial will be needed to assess the effects of early rehabilitation and it may be that this sort of trial will never be performed owing to the methodological problems I have encountered. A simpler trial design will be needed, as discussed above, perhaps simply investigating NMS vs. usual care and using simple assessments such as quality of life, 6MW, neurohormonal markers of severity of CHF, and possibly not including cardiopulmonary data. Of note is that relatively few trials of exercise training in CHF have included specific reference to the involvement of heart failure specialist nurse involvement. It is well recognised that CHF nurse liaison is an effective intervention in CHF with respect to hospital admission rates and survival (Blue *et al.*, 2001; Rich *et al.*, 1995; Stewart *et al.*, 1999). CHF nurses provide education, motivation and close

monitoring of clinical state for CHF patients. We were careful to control for this by including nurse support in study 4. It is not clear whether the additional monitoring provided by study investigators during CHF exercise-training trials is equivalent, better or less useful than CHF specialist nurse support, but it will be important to remember that the control group's usual care for some research studies may in fact be less good than the current gold standard which includes heart failure nurse liaison support.

10 Conclusions

There is no doubt that in selected CHF patients, exercise training is safe, beneficial and worthwhile. The major conceptual hurdle, though, is that the heart failure population is elderly, symptomatic and demotivated. Exercise training trials are by necessity of an open design and there may of course be a large placebo effect following exercise regimes and this should be considered when interpreting the results of quality of life measures and submaximal exercise performance parameters, e.g., 6MW. There is little question, however, that qualitative changes do occur following training, such as improvement in aerobic capacity and attenuation of the pro-inflammatory response. How do we translate these potential gains from the highly selected CHF trial patient to the wider CHF population? I know from my own data, presented in chapter 8, that the CHF trial patient is younger, more likely to be male and likely already to be taking some form of regular exercise prior to enrolment in the study when compared with the very much larger group of non-eligible patients. This makes extrapolation of data difficult and it is hard to recommend training to, for instance, elderly female CHF patients on this basis.

NMS may be an effective option to provide exercise training to the wider CHF population as, I believe, it is easier to perform than conventional exercise and, as can be seen from studies 1, 3 and 4, beneficial changes following NMS training are observed. I do not think that the stimulation protocol used or duration of training performed was optimal and this is reflected by the minimal change in peak VO_2 observed following NMS and indeed with conventional training. Additionally, a wider CHF population

needs to be targeted to allow sensible extrapolation of these findings before recommendation of NMS training can be made.

The recruitment of recently decompensated patients in study 4 (chapter 7) was ambitious but, as it subsequently proved, useful. The high rate of dropout emphasised that a much larger trial would be required to assess the effect of NMS in this population. Since this type of trial is unlikely to be repeated even on a small scale, however, training will continue to be recommended for stable patients only. This is unfortunate as NMS training may be effective in this population and may indeed serve as a bridging therapy before a more conventional regime can be undertaken.

I sincerely hope that work in this area continues. Trials of exercise training have tended to recruit small numbers of patients in the past and in the era of modern CHF management, pharmacological and device therapy will dilute the potential benefits seen in such small trials. Additionally, non-patentable treatments such as NMS (and exercise in general) will struggle to attract funding for large scale clinical trials. Without the large trials, we will not be able to confirm the new concepts in exercise therapy that emerge with the smaller, ambitious study.

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Appendix A. Minnesota Living with Heart Failure Questionnaire

The following questions ask how much your heart failure (heart condition) affected your life during the past month (4 weeks). After each question, circle the 0, 1, 2, 3, 4 or 5 to show how much your life was affected. If a question does not apply to you, circle the 0 after that question.

Did your heart failure prevent you from living as you wanted during the past month (4 weeks) by -		No	Very little				Very much
1	causing swelling in your ankles or legs?	0	1	2	3	4	5
2	making you sit or lie down to rest during the day?	0	1	2	3	4	5
3	making your walking about or climbing stairs difficult?	0	1	2	3	4	5
4	making your working around the house or yard difficult?	0	1	2	3	4	5
5	making your going places away from home difficult?	0	1	2	3	4	5
6	making your sleeping well at night difficult?	0	1	2	3	4	5
7	making your relating to or doing things with your friends or family difficult?	0	1	2	3	4	5
8	making your working to earn a living difficult?	0	1	2	3	4	5
9	making your recreational pastimes, sports or hobbies difficult?	0	1	2	3	4	5
10	making your sexual activities difficult?	0	1	2	3	4	5
11	making you eat less of the foods you like?	0	1	2	3	4	5
12	making you short of breath?	0	1	2	3	4	5
13	making you tired, fatigued, or low on energy?	0	1	2	3	4	5
14	making you stay in a hospital?	0	1	2	3	4	5
15	costing you money for medical care?	0	1	2	3	4	5
16	giving you side effects from treatments?	0	1	2	3	4	5
17	making you feel you are a burden to your family or friends?	0	1	2	3	4	5
18	making you feel a loss of self-control in your life?	0	1	2	3	4	5
19	making you worry?	0	1	2	3	4	5
20	making it difficult for you to concentrate or remember things?	0	1	2	3	4	5
21	making you feel depressed?	0	1	2	3	4	5

Instructions for Data Collection and Scoring

1. Patients should respond to the questionnaire prior to other assessments and interactions that may bias their responses. You might tell the patient that you would like to get his or her opinion before doing your medical assessment.
2. Ample, uninterrupted time should be provided for the patient to complete the questionnaire. We recommend that the patient answer the questions without being influenced by others such as their spouse or family members. Studies show that patient proxies often have different perspectives.
3. We recommend that you use the first question to give the respondent more detailed instructions as follows.
 - a. Read the introductory paragraph at the top of the questionnaire.
 - b. Read the first question with the respondent – “Did your heart failure prevent you living as you wanted during the last month (4 weeks) by causing swelling in your ankles or legs?” Then tell the respondent -
 - If you did not have any ankle or leg swelling during the past month (4 weeks) you should circle the zero (0) after this question.
 - If you did have swelling that was caused by a sprained ankle or some other cause that you are sure was not related to heart failure, you should circle the zero (0) after this question.
 - If you had swelling that might be related to your heart condition, then rate how much the swelling prevented you from doing things you wanted to do or feeling the way you would like to feel. In other words, how much did the swelling affect your life? Circle either the 0, 1, 2, 3, 4 or 5 to indicate how much the swelling affected your life during the past month – zero (0) means not at all, one (1) means very little and five (5) very much.
4. Ask the patient read and respond to all 21 questions. The entire questionnaire may be read directly to the patient if one is careful not to influence responses by verbal or physical cues.

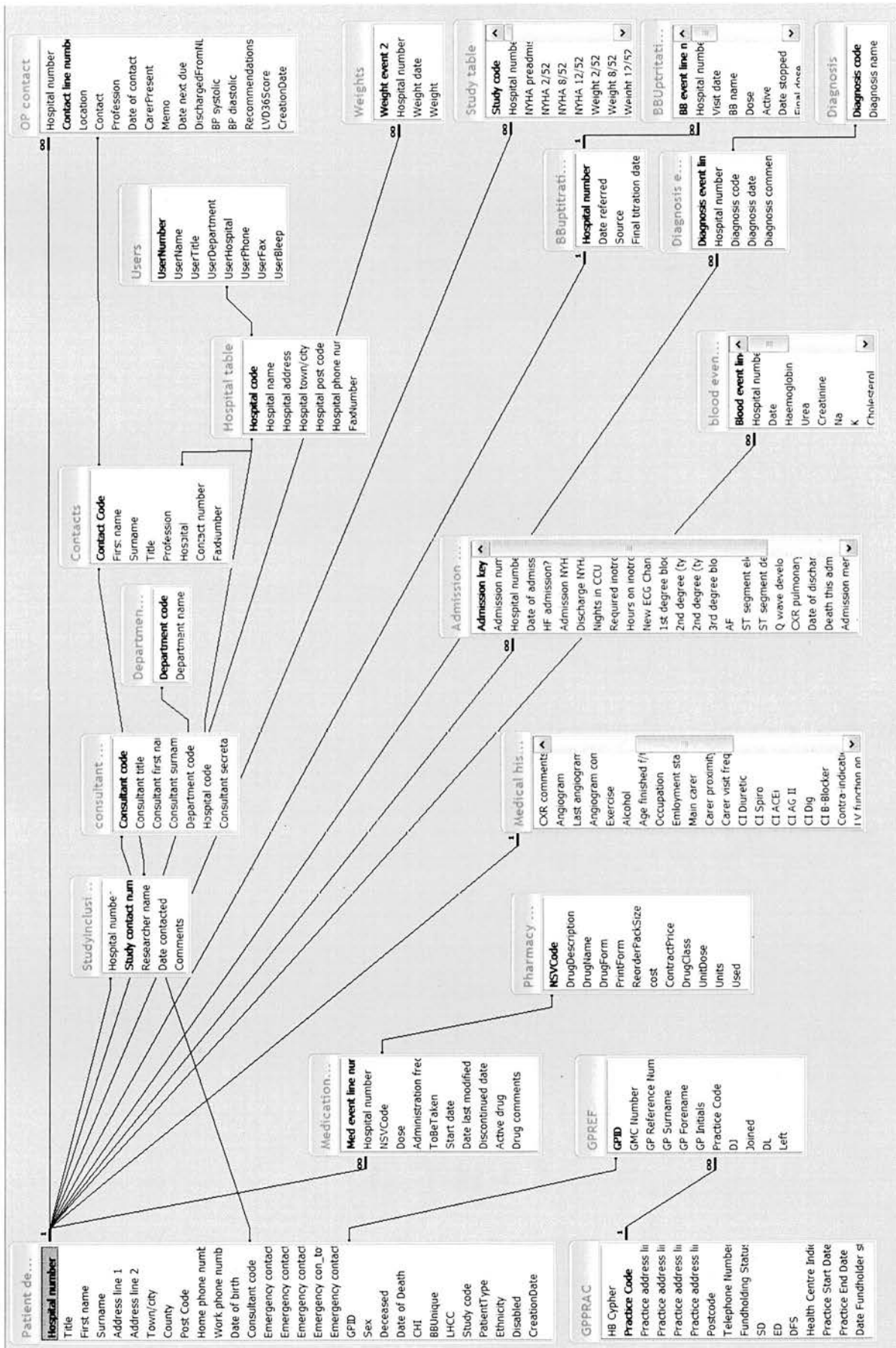
5. Check to make sure the patient has responded to each question. If a question does not apply to the patient they should circle the zero (0). Make sure there is only one answer clearly marked for each question.
6. Score the questionnaire by summing the responses to all 21 questions. In addition, a physical dimension score (items 2, 3, 4, 5, 6, 7, 12, 13 on the version sent with these instructions) and emotional dimension score (items 17, 18, 19, 20, 21) have been identified by factor analysis and may be scored by simple summation to further characterize the effect of heart failure on a patient's life.
7. Partially complete questionnaires do occur despite best efforts to minimize missing data. However, missing data can greatly bias the data and complicate analysis. To reiterate, you need to make sure the respondents understand to mark zero for any items that do not apply to them, rather than leave a blank. Whenever possible review the questionnaire before the respondent leaves to make sure there are no unanswered questions or questions with more than one answer.
8. Several methods to impute missing data are discussed in the literature.^{1,2} Multiple imputation using completed questions and perhaps other study variables to predict missing responses should be considered.³ If a missing response is not imputed, the item will be eliminated from that person's score (the sum of responses). Since intermittently missing data can greatly affect within-person changes in scores, you might want to use the same subset of questions to represent a person at all times by omitting questions that have missing data at any point in time. We do not have any recommendations about when missing data become too extensive to render the information being collected useless.

¹ Fayers PM et al. Incomplete quality of life data in randomized trials: missing items. *Statistics in Medicine* 1998;17:679-696.

² Schaffer JL and Graham JW. Missing data: our view of the state of the art. *Psychological Methods* 2002;7:147-177.

³ Raghunathan TE, et al. A multivariate technique for multiply imputing missing values using a sequence of regression models. *Survey Methodology* 2001;27:85-95.

Appendix B. Database relationships



Appendix C. Diagnosis list

Diagnosis code	Diagnosis name
1	Acromegaly
2	Acute renal failure
3	Addison's disease
4	AIDS related complex
5	Alcohol excess
6	Alcoholic liver disease
7	Alzeimhers disease
8	Amlyoid heart disease
9	Amputation
10	Anaemia
11	Angina
12	Angioplasty
13	Anomalous pulmonary venous drainage - partial
14	Aortic aneurysm (abdominal)
15	Aortic aneurysm (thoracic)
16	Aortic Aneurysm Repair
17	Aortic regurgitation
18	Aortic stenosis
19	Aortic stenosis (severe)
20	Aortic valve replacement
21	Asbestosis
22	Asthma
23	Asymmetrical paraparesis
24	Asystolic arrest
25	Atrial fibrillation (paroxysmal)
26	Atrial fibrillation (permanent)
27	Atrial flutter
28	Atrial septal defect
29	Atrial septal defect - closure
30	Benign prostatic hypertrophy
31	Bowel obstruction
32	Bronchiectasis
33	CABG
34	Carcinoma - bladder
35	Carcinoma - breast
36	Carcinoma - bronchus
37	Carcinoma - colon
38	Carcinoma - endometrium
39	Carcinoma - kidney
40	Carcinoma - liver
41	Carcinoma - lung

- 42 Carcinoma - melanoma
- 43 Carcinoma - oesophagus
- 44 Carcinoma - ovary
- 45 Carcinoma - pancreas
- 46 Carcinoma - prostate
- 47 Carcinoma - stomach
- 48 Carcinoma- Laryngeal
- 49 Cardiac Failure
- 50 Cardiac tamponade
- 51 Cardiogenic shock
- 52 Cardiomyopathy - dilated
- 53 Cardiomyopathy - hypertrophic
- 54 Cardiomyopathy - restrictive
- 55 Cardioversion - successful
- 56 Cardioversion - unsuccessful
- 57 Carotid Endarterectomy
- 58 Chest infection
- 59 Chronic fatigue syndrome
- 60 Chronic lymphatic leukaemia
- 61 Chronic myeloid leukaemia
- 62 Chronic renal failure
- 63 Chronic renal impairment (mild)
- 64 Chronic renal impairment (moderate)
- 65 Chronic renal impairment (severe)
- 66 Coarctation of the aorta
- 67 Coeliac disease
- 68 COPD
- 69 Cor pulmonale
- 70 Coronary artery bypass
- 71 Coronary artery bypass, 1 vessel
- 72 Coronary artery bypass, 2 vessels
- 73 Coronary artery bypass, 3 vessels
- 74 Coronary artery bypass, 4 vessels
- 75 Coronary artery bypass, 5 vessels
- 76 Coronary artery disease
- 77 Coronary stent
- 78 Crohn's disease
- 79 Cushing's disease
- 80 Cushing's syndrome
- 81 CVA
- 82 Dementia
- 83 Depression
- 84 Dermatitis herpetiformis
- 85 Diabetes mellitus type I
- 86 Diabetes mellitus type II
- 87 Diabetic nephropathy
- 88 Diabetic retinopathy

- 89 Diverticular disease
- 90 Down Syndrome
- 91 Duodenal Ulcer
- 92 DVT
- 93 Eczema
- 94 Embolus
- 95 EMD arrest
- 96 Encephalitis
- 97 Endocarditis
- 98 Epilepsy
- 99 Erectile dysfunction
- 100 Femoral popliteal bypass
- 101 Gastric angio-dysplasia
- 102 Giant cell arteritis
- 103 Glaucoma
- 104 Glomerulonephritis
- 105 Glucocorticoid suppressible hyperaldosteronism
- 106 GORD
- 107 Gout
- 108 Heart block (complete)
- 109 Heart block (type I second degree)
- 110 Heart block (type II second degree)
- 111 Heart transplant
- 112 HIV
- 113 Hodgkin's lymphoma
- 114 Hypercholesterolaemia
- 115 Hyperparathyroidism (primary)
- 116 Hyperparathyroidism (secondary)
- 117 Hyperparathyroidism (tertiary)
- 118 Hypertension
- 119 Hyperthyroidism
- 120 Hypertriglyceridaemia
- 121 Hypopituitarism
- 122 Hypothyroidism
- 123 Ileo-Femoral Bypass
- 124 Implantable cardiac defibrillator
- 125 Infective endocarditis
- 126 Intermittent Claudication
- 127 Intracranial Acoustic Neuroma
- 128 Irritable bowel syndrome
- 129 Ischaemic Heart Disease
- 130 Ischaemic heart disease - angina
- 131 Kaposi sarcoma
- 132 Knee Replacement
- 133 Left Ventricular Systolic Dysfunction
- 134 Left Ventricular Systolic Dysfunction - Mild
- 135 Left Ventricular Systolic Dysfunction - Mild/Mod

- 136 Left Ventricular Systolic Dysfunction - Mod/Severe
- 137 Left Ventricular Systolic Dysfunction - Moderate
- 138 Left Ventricular Systolic Dysfunction - Severe
- 139 Leukaemia
- 140 Libman-Sacks endocarditis
- 141 Malaria
- 142 Meningitis
- 143 Meningo-encephalitis
- 144 Migraine
- 145 Mitral regurgitation
- 146 Mitral stenosis
- 147 Mitral valve prolapse
- 148 Mitral valve replacement
- 149 Mixed aortic valve disease
- 150 Mixed connective tissue disease
- 151 Mixed mitral valve disease
- 152 Motor neurone disease
- 153 Multiple sclerosis
- 154 Myeloma
- 155 Myeloproliferative disorder
- 156 Myocardial Infarction
- 157 Myocardial infarction - non Q wave
- 158 Myocardial infarction - Q wave
- 159 Narcolepsy
- 160 Nephrectomy
- 161 Non ulcer dyspepsia
- 162 Non-hodgkins Lymphoma
- 163 Obesity
- 164 Oesophageal stricture
- 165 Osteoarthritis
- 166 Osteoporosis
- 167 Paget's disease
- 168 Pancreatitis (acute)
- 169 Pancreatitis (chronic)
- 170 Paraplegia
- 171 Parathyroidectomy
- 172 Parkinson's disease
- 173 Paroxysmal Tachycardia
- 174 Pathway ablation
- 175 PCI
- 176 Peptic ulcer disease
- 177 Pericardectomy
- 178 Pericarditis (constrictive)
- 179 Pericarditis (inflammatory)
- 180 Peripheral neuropathy
- 181 Peripheral vascular disease
- 182 Permanent Pacemaker

- 183 Permanent pacemaker (biventricular)
- 184 Permanent pacemaker (dual chamber)
- 185 Permanent pacemaker (single chamber)
- 186 Pernicious Anaemia
- 187 Pneumonia
- 188 Polycythaemia rubra vera
- 189 Polymyalgia rheumatica
- 190 Postural Hypotension
- 191 Previous cholecystectomy
- 192 Prostate Problems
- 193 Psoriasis
- 194 Psychosis
- 195 Pulmonary embolism - single
- 196 Pulmonary embolism - recurrent
- 197 Pulmonary fibrosis
- 198 Pulmonary hypertension
- 199 Renal Angioplasty
- 200 Renal artery stenosis
- 201 Renal impairment
- 202 Respiratory failure
- 203 Restrictive lung disease
- 204 Rheumatoid arthritis
- 205 Schizophrenia
- 206 Sciatica
- 207 Scoliosis
- 208 Sick sinus syndrome
- 209 sleep apnoea
- 210 Steven Johnson Syndrome
- 211 Still's disease
- 212 Stroke
- 213 Subarachnoid haemorrhage
- 214 Supra ventricular tachycardia
- 215 Syncope
- 216 Systemic lupus erythematosus
- 217 Tachycardia (paroxysmal)
- 218 Tachycardia (permanent)
- 219 TB
- 221 Temporal arteritis
- 222 Thrombus - left ventricle
- 223 Thrombus - right ventricle
- 224 Transient ischaemic attack
- 225 Trans-urethral resection of prostate
- 226 Tricuspid regurgitation
- 227 Tricuspid valve replacement
- 228 Ulcerative colitis
- 229 Urinary Catheter
- 230 Urinary tract infection - recurrent

- 231 Valvuloplasty - mitral
- 232 Vasculitis (not specified)
- 233 Ventricular aneurysm
- 234 Ventricular standstill
- 235 Ventricular tachycardia
- 236 Vertebrobasilar insufficiency
- 237 VF / VT arrest
- 238 VSD